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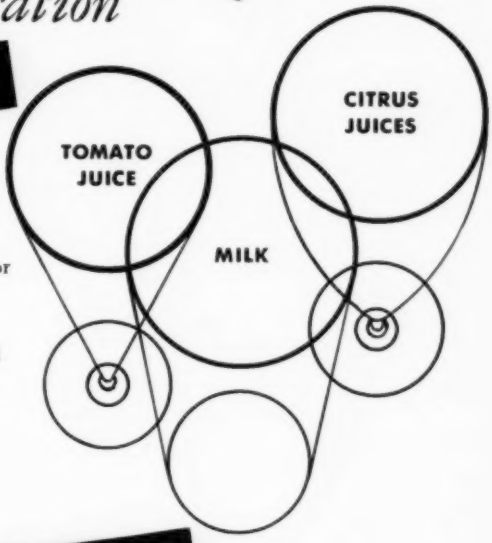

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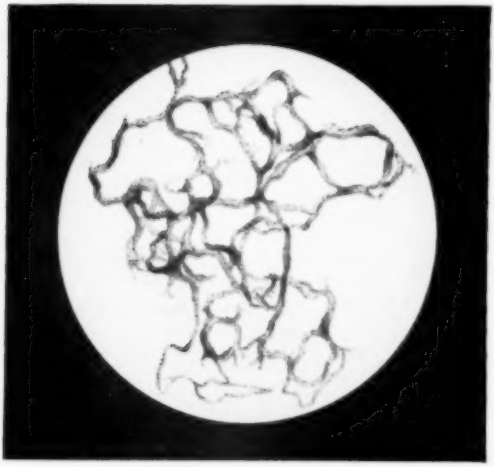

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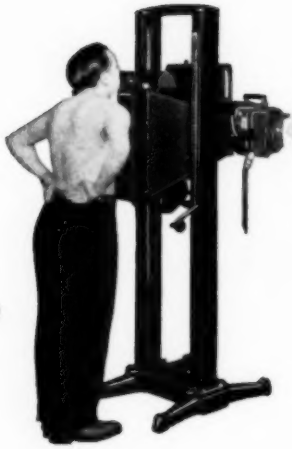

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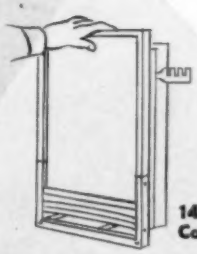

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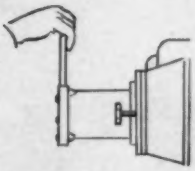

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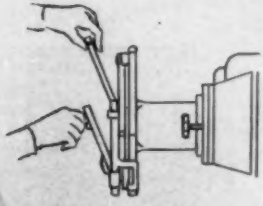

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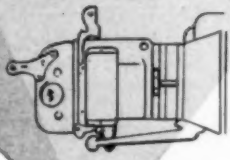

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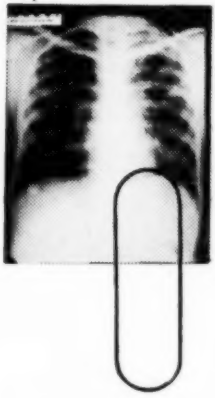

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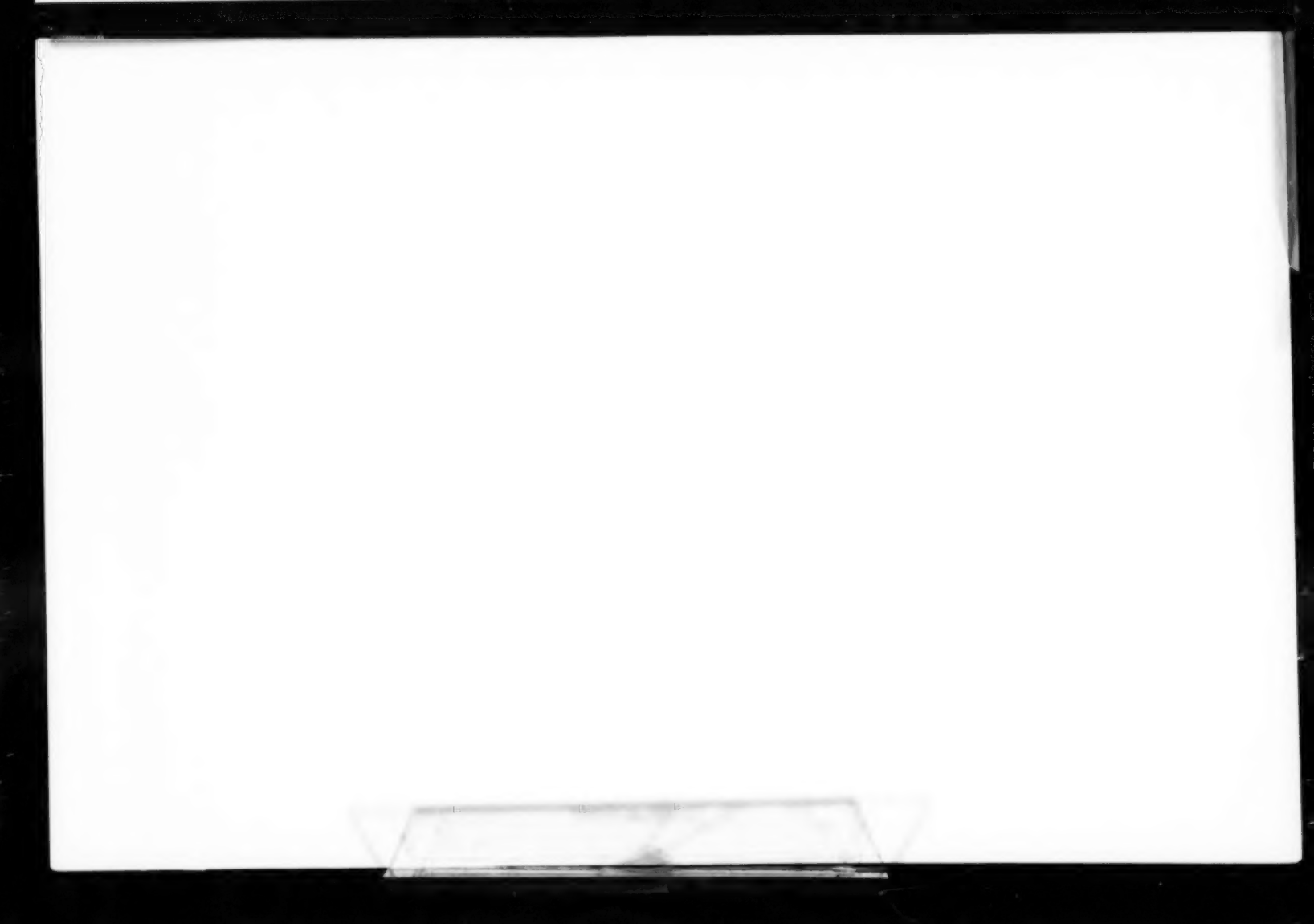

THE AMERICAN REVIEW
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VOLUME 66 *November 1952* NUMBER 5

A BRONCHOSPIROMETRIC STUDY OF PULMONARY FUNCTION AFTER DECORTICATION IN PULMONARY TUBERCULOSIS[1, 2, 3]

ABRAHAM FALK, ROY T. PEARSON, AND FRANK E. MARTIN

(Received for publication May 28, 1952)

INTRODUCTION

A number of reports have appeared within recent years concerning the clinical and physiologic effects of decortication of the lung, chiefly following traumatic hemothorax and complications of tuberculosis (1–4). Very complete studies of total pulmonary function have been reported both preoperatively and postoperatively for many of these cases. Nevertheless, bronchospirometric determinations both before and after decortication for various complications of pneumothorax and pleural involvement in pulmonary tuberculosis have been few.

PLAN OF STUDY

A series of 13 decortications in pulmonary tuberculosis with preoperative and postoperative bronchospirometric determinations, as well as one additional postoperative study only, done at this hospital is the basis for the present report. Nine cases presented the syndrome of unexpandable lung following artificial pneumothorax; 4, the sequelae of tuberculous pleurisy with effusion; and one, tuberculous pyopneumothorax following surgical excision of a tuberculous costal cartilage. Laboratory facilities for the determination of lung volume and other studies requiring gas analyses were not available during the first portion of the study, and such subsequent data have not been included in this report.

All patients in this series were male, ranging between twenty-two and sixty years of age. Significant clinical data, particularly those pertaining to duration of pneumothorax or effusion prior to decortication, are contained in table 1. Pneumothorax had existed for fifteen months to thirteen years, and the lung had

[1] From the Veterans Administration Hospital, Department of Medicine, and the University of Minnesota Medical School, Minneapolis, Minnesota.

[2] Presented before the Medical Section, as part of the *Surgical Session on Tuberculosis*, at the 48th annual meeting of the National Tuberculosis Association, Boston, Massachusetts, on May 28, 1952.

[3] Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

been considered unexpandable for four months to ten years prior to decortication. The duration of pleurisy with effusion prior to decortication was much shorter.

Bronchospirometry was done within a month prior to decortication in most instances and repeated five to eight months following surgery. The method employed was the usual one of introduction of a Zavod double-lumen catheter under local laryngeal anesthesia, placement of the catheter under fluoroscopic control with inflation of the cuffs, and attachment to double recording spirometers (McKesson) filled with 100 per cent oxygen. Bronchoscopy was done in every case prior to bronchospirometry, but the procedures were not combined.

The decortication in each instance involved removal of both the visceral and parietal "peel." In 4 cases of unexpandable lung following pneumothorax, an associated small thoracoplasty was done to maintain collapse of the diseased upper lobe and the remainder was decorticated to fill the space (table 1). In one of these cases (P. V.), a hemothorax occurred subsequent to surgery and secondary decortication was necessary approximately six weeks later. Another patient (M. F.) had a right upper lobe lobectomy, five-rib thoracoplasty, and decortication of the remaining lobes. Other than the hemothorax noted above, there were no complications in the series. All patients received streptomycin, or streptomycin and PAS, during the surgical period, usually for approximately three weeks.

Histologic study of the decorticated tissue was done in each instance.

OBSERVATIONS

In 3 of the 4 patients with pleurisy with effusion (S. B., M. B., A. H.), active tubercles were found to be scattered in the decorticated tissue, but this finding was present in only one of the pneumothorax group. In the remainder of the entire series, chronic inflammatory tissue or fibrous pleuritis was the only residual.

Three cases described in greater detail are characteristic of the problems and course in the entire group. The fourth case is unusual in that the surgical approach to an unexpanded lung of ten years' duration resulted in restoration of sufficient function to allow excisional surgery on the contralateral side.

Illustrative Cases

W. T., a 24-year-old white male, was found to have active left apical pulmonary tuberculosis in July, 1947. A left pneumothorax was instituted in October, 1947, and continued, but the patient was not hospitalized. In August, 1948, there was sudden onset of hydrothorax and aspirated fluid was positive for tubercle bacilli on culture. Subsequent attempts at re-expansion of the lung were unsuccessful.

The patient was admitted to this hospital on December 28, 1948 (figure 1*A*), and decortication of the visceral and parietal "peel" from the entire lung and diaphragm was done on January 24, 1949, with good expansion (figure 1*B*). The "peel" varied from 0.25 cm. to 0.5 cm. in thickness and on histologic examination revealed fibrous tissue containing scattered tubercles. The postoperative course was uneventful, and he was discharged on April 18, 1950 (figure 1*C*). All bacteriologic studies following surgery were negative.

Comment: Bronchospirometric studies two months after decortication revealed moderate improvement in ventilation but little in oxygen uptake. The results

TABLE 1

CLINICAL AND LABORATORY DATA

CASE	AGE	DURATION PRIOR TO SURGERY			ACID-FAST BACILLI IN FLUID	DIAPHRAGM MOBILITY*		BRONCHOSPIROMETRY		CONCOMITANT THORACOPLASTY
		Pneumothorax	Effusion	"Bound" Lung		Preoperatively	Postoperatively	Preoperatively	Postoperatively	
	years	*months*	*months*	*months*				*months*	*months*	
M. K.	22	33	18	11	—	Minimal	Moderate	1	8	5-rib
W. T.	24	15	5	4	Present	Minimal	None	1 day	8	
P. V.	35	25	24	14	Present	Minimal	Minimal	2	8	4-rib
C. G.	31	47	41	8	Absent	Minimal	None	15 days	6	
J. R.	25	62	—	10	—	Minimal	Minimal	1 day	6	4-rib
G. D.	26	58	2	6	Absent	Moderate	Moderate	1	6	
W. C.	60	13 years	10 years	10 years	Absent	None	None	7	5	
C. T.	31	74	22	22	Absent	Minimal	Minimal	1	5	3-rib
M. F.	30	43	35	24	Present	Moderate	Normal	3	6	5-rib with right upper lobe lobectomy
S. B.	50		8		Present	Minimal	Moderate	6	8	
A. H.	33		13		Present	None	Minimal	1	6	
J. O.	25		30		Absent	Moderate	Moderate	11	6	
M. B.	40		6		Absent	Minimal	Moderate	1	6	
D. H.	23		4		Present	Moderate	Moderate	—	9	

* Decorticated side.
Minimal—1 to 2 cm.
Moderate—2 to 4 cm.
Normal—4+ cm.

are almost identical with those obtained one year following surgery, indicating no improvement in pulmonary efficiency of the decorticated lung during that period.

J. R., a 25-year-old white male, was found to have active pulmonary tuberculosis involving the right upper lobe with cavitation in July, 1945. Right pneumothorax was instituted in September, 1945, and was followed by a pneumonolysis in October, 1945, which was complicated by hydrothorax of short duration. All bacteriologic studies became negative for *M. tuberculosis* following the pneumothorax. Refills were continued, but attempts at re-expansion of the lung early in 1950 were unsuccessful.

The patient was admitted to this hospital on October 9, 1950 (figure 2*A*), and decortication of both visceral and parietal "peel" over the middle and lower lobes of the right lung and diaphragm was done on November 9, 1950. Simultaneous four-rib thoracoplasty was done to maintain permanent collapse of the right upper lobe (figure 2*B*). The "peel" averaged 0.5 cm. in thickness and histologically revealed only fibrous tissue. The postoperative course was uneventful, his secretions remained negative for tubercle bacilli, and he was discharged on August 7, 1951.

Comment: Bronchospirometry six months after decortication and thoracoplasty revealed slight diminution in vital capacity and minute ventilation, but no change in oxygen uptake.

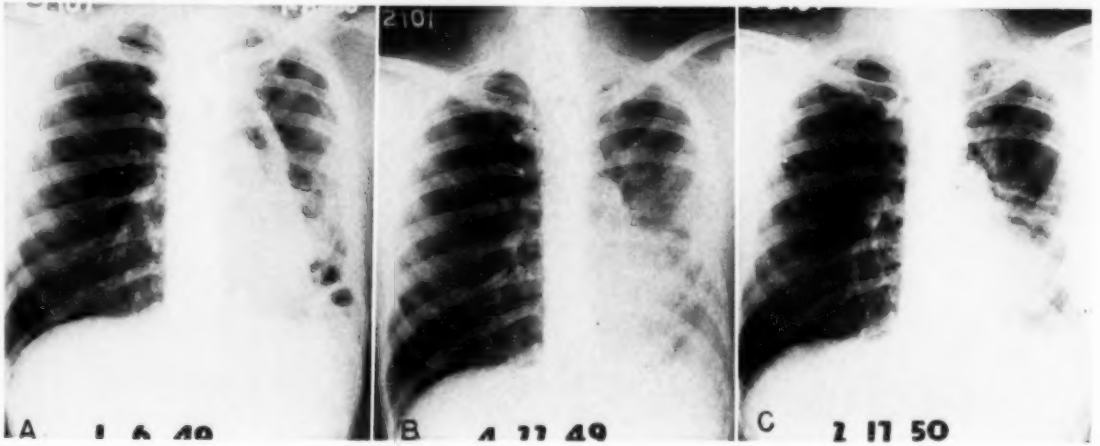
A. H., a 33-year-old white male, had an acute right pleurisy with effusion in March, 1949 (figure 3*A*), for which he was hospitalized elsewhere. Weekly aspirations of pleural fluid were necessary in amounts of 100 to 1,600 cc., and hydropneumothorax was present continuously after thoracenteses were begun. Cultures of the fluid were positive for tubercle bacilli. One gastric culture was positive for tubercle bacilli.

The patient was admitted to this hospital on February 21, 1950, and was found to have a "bound" lung with considerable pleural effusion (figure 3*B*). Decortication of the visceral and parietal "peel" over the entire right lung and diaphragm was done on April 5, 1950, with good re-expansion. The "peel" measured 0.3 to 0.6 cm. in thickness and on histologic examination revealed fibrous tissue with scattered tubercles. The postoperative course was uneventful, and the sputum and gastric cultures remained negative for tubercle bacilli throughout the period of hospitalization. No evidence of parenchymal involvement was noted on chest films (figure 3*C*) or at surgery. The patient was discharged on January 15, 1951.

Comment: Bronchospirometry six months after decortication revealed a marked increase (50 per cent) in vital capacity and, to a lesser extent (18 per cent), in minute ventilation, but oxygen uptake remained essentially unchanged from the preoperative findings. No evidence of parenchymal involvement was noted.

W. C., a 60-year-old white male, had had a known tuberculous lesion in the right apex since 1930. Reactivation, with cavitation, was found in January, 1937, and a right pneumothorax instituted with ineffective collapse (figure 4*A*). The patient left the hospital in November, 1937, to remain under the care of his physician. He was rehospitalized in 1938, and subsequently had a four-rib thoracoplasty on the right, but the pneumothorax was maintained. Hydrothorax was present during and after 1940, but cultures of the fluid were negative for *M. tuberculosis*. Cultures of sputum were negative for tubercle bacilli following surgery, and the patient again returned to the care of his physician in 1941. Oleothorax was attempted in 1946 to fill the pleural space but was abandoned due to reaction. The pneumothorax was continued, and the lung was markedly collapsed and "bound" after 1940.

The patient remained well and working until early in 1949, when a cavity was noted in the

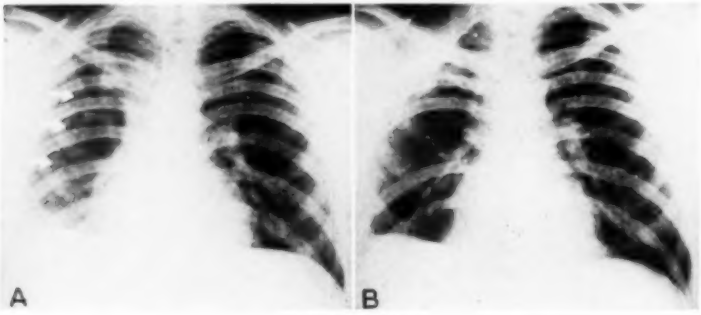


Case 1 (W. T.)

FIG. 1. *A*. Chest roentgenogram which reveals pneumothorax of fifteen months' duration.
B. Chest roentgenogram taken three months after decortication.
C. Chest roentgenogram taken one year after decortication.

third left interspace, but without the discharge of tubercle bacilli in the sputum. He was readmitted to this hospital on July 8, 1949. Numerous sputum and gastric cultures were negative for tubercle bacilli, and only one isolated smear of sputum concentrate was reported positive for acid-fast bacilli throughout the period of hospitalization. The cavity did not decrease in size (figure 4*B*), and possible resection was contraindicated due to the almost complete lack of oxygen uptake by the right lung. Decortication of the right lung was done on May 4, 1950, with removal of the parietal and visceral "peels" from the right middle and lower lobes. The "peel" was 1 to 3 mm. thick and on histologic examination revealed only fibrous tissue. The thoracoplasty was not disturbed, and the lung expanded to fill the space (figure 4*C*). The surgical and postoperative periods were remarkably uneventful.

A marked improvement (30 per cent) in oxygen uptake by the right lung was noted following decortication, and on December 20, 1950, a wedge resection in the left upper lobe was performed and a tuberculous cavity 1 cm. in diameter, together with active satellite nodular tuberculosis, was removed. Streptomycin, 1 gm. twice per week, and PAS, 12 gm. daily,



Case 2 (J. R.)

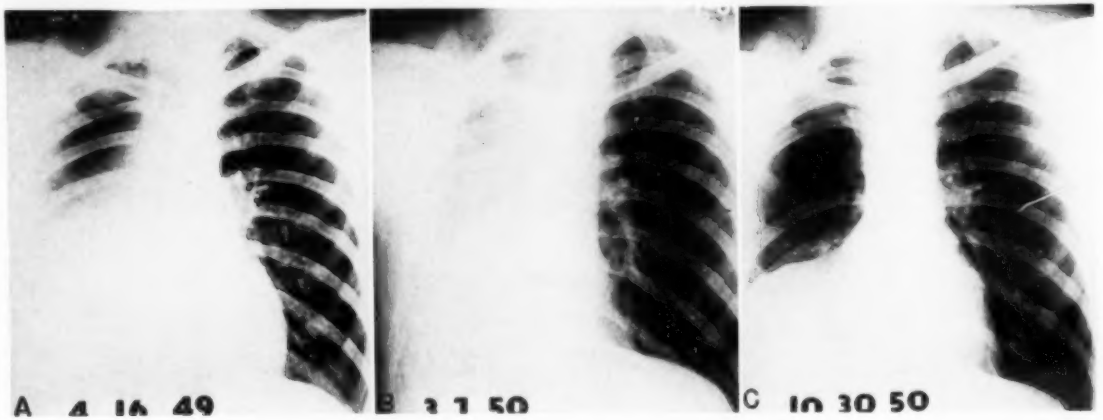
FIG. 2. *A*. Chest roentgenogram which reveals pneumothorax of five years' duration. *B*. Chest roentgenogram taken six months after decortication and four-rib thoracoplasty.

were given for the three-week surgical period. The surgical and postoperative periods were uneventful. The patient was discharged on August 30, 1951 (figure 4*D*).

Comment: Decortication achieved closure of the pleural space by re-expansion of the right lung after thirteen years in addition to restoration of sufficient function (oxygen uptake) to make possible resectional surgery on the left. Ventilation and minute volume were only slightly increased. Considerable functioning lung tissue evidently remained despite the almost complete collapse of long duration.

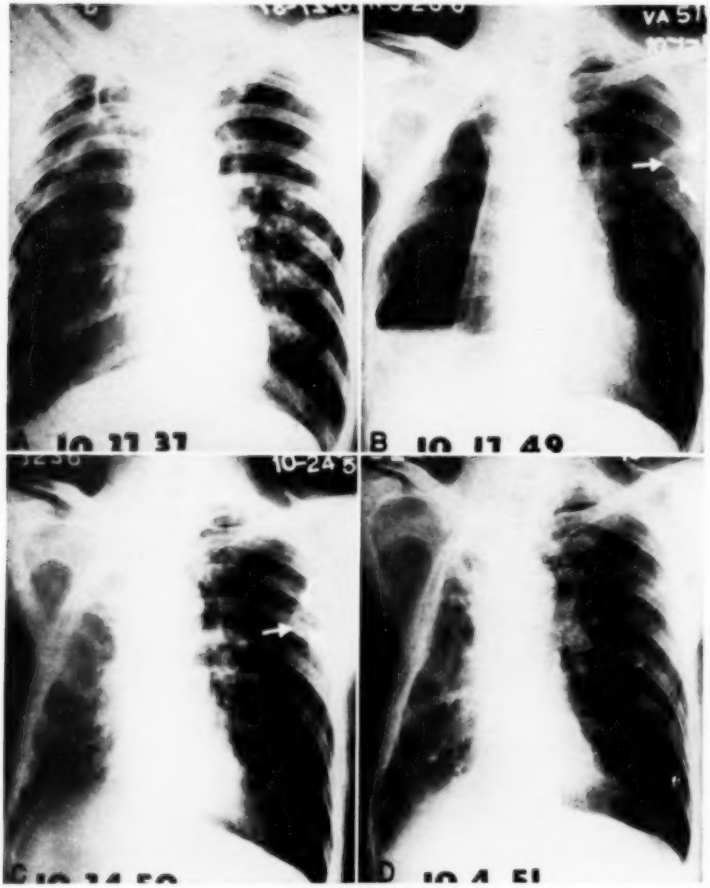
Results of the Studies of Pulmonary Function

The data obtained from the functional studies are listed in table 2. These are expressed as percentages of total vital capacity, oxygen uptake, and minute ventilation on the involved side, both before and after decortication. The total value (both lungs) for each division of pulmonary function is also shown. It was believed that little could be gained from an analysis of individual variations but that comparison of the means of each group of determinations might express



Case 3 (A. H.)

FIG. 3. *A*. Chest roentgenogram taken one month after onset of pleurisy with effusion.
B. Chest roentgenogram taken one month before decortication.
C. Chest roentgenogram taken six months after decortication.



Case 4 (W. C.)

FIG. 4. *A*. Chest roentgenogram taken two months after institution of right pneumothorax.

B. Chest roentgenogram taken on admission, showing recent cavity in left upper lobe and contralateral thoracoplasty and oleo-pneumothorax of twelve years' duration.

C. Chest roentgenogram taken two weeks after decortication showing persistent cavitation on left.

D. Chest roentgenogram taken ten months following wedge resection of cavity in left upper lobe.

significance. The group of pneumothorax cases was also analyzed separately from the pleurisy with effusion group since, in the latter group, there was no demon-

TABLE 2

BRONCHOSPIROMETRIC DETERMINATIONS OF PULMONARY FUNCTION, BEFORE AND AFTER DECORTICATION, EXPRESSED AS PERCENTAGE CONTRIBUTED BY THE INVOLVED LUNG

CASE	SIDE	VITAL CAPACITY				OXYGEN UPTAKE				VENTILATION (RMV)			
		Preoperatively		Postoperatively		Preoperatively		Postoperatively		Preoperatively		Postoperatively	
		Per cent	Total cc.*	Per cent	Total cc.	Per cent	Total cc.	Per cent	Total cc.	Per cent	Total cc.	Per cent	Total cc.
Unexpandable Lung (Pneumothorax)													
M. K.	Right	35	1,425	37	2,550	21	460	37	338	40	5,800	49	6,500
W. T.	Left	8	1,280	20	3,000	30	386	34	333	14	4,350	24	3,150
P. V.	Left	23	1,100	22	1,400	12	301	13	307	27	5,225	40	10,500
C. G.	Left	19	3,100	23	4,100	16	325	33	375	33	4,200	43	7,400
J. R.	Right	45	1,800	41	2,550	33	450	32	317	52	4,800	40	9,800
G. D.	Right	63	1,900	49	3,200	56	416	47	400	55	4,400	58	7,680
W. C.	Right	19	1,300	25	2,150	2	610	32	491	30	6,900	32	7,100
C. T.	Right	28	2,500	27	2,200	23	280	25	200	35	4,800	41	6,000
M. F.	Right	34	730	32	1,440	20	207	48	180	33	6,300	38	7,400
Mean and S.D.		30.4 ± 16.3		30.6 ± 9.7		23.7 ± 15.2		33.4 ± 10.6		35.4 ± 12.5		40.6 ± 9.6	
Difference		0.22 ± 7.22				9.7 ± 13.6				5.2 ± 7.4			
Pleurisy with Effusion													
S. B.	Left	29	2,100	36	1,700	25	300	36	387	43	7,200	40	7,250
A. H.	Right	7	3,000	57	2,800	36	508	38	450	15	10,200	33	7,100
J. O.	Left	13	2,300	21	2,400	25	441	33	540	30	4,450	48	6,300
M. B.	Left	22	2,500	39	2,950	26	470	39	341	33	12,000	38	11,025
Mean and S.D.		17.8 ± 9.7		38.2 ± 14.7		28.0 ± 5.3		36.5 ± 2.7		30.3 ± 11.6		39.8 ± 6.0	
Difference		20.4 ± 20.17				8.5 ± 4.8				9.5 ± 17.92			
Tuberculous Pyopneumothorax													
D. H.	Right			42	3,400			49	550			42	17,400

* Total of both lungs.

strable pulmonary involvement by roentgenography, the process was primarily active in the pleura, and the period preceding surgery was much shorter than in the group of pneumothorax complications.

Because of the small number of cases in each group, it was believed that comparison of the mean differences within each group and between the two groups would have more validity than comparison by testing for statistical significance. These differences are shown in table 2 and are graphically expressed in figure 5. Nevertheless, tests for statistical significance were applied to the entire group of 13 cases, and the improvement in oxygen uptake and ventilation was found to be significant ($p = 0.02$). Similar testing for changes in vital capacity was not considered valid since the difference in the pneumothorax group was negligible

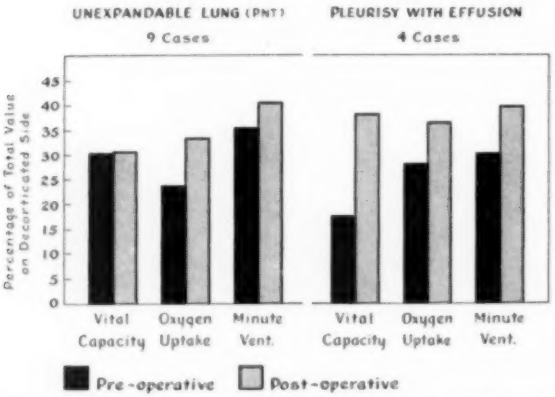


FIG. 5. Graphic presentation of differences in lung function noted in table 2. Oxygen uptake and minute ventilation are improved to approximately the same extent in each group but with vital capacity markedly improved in the pleurisy with effusion group.

and that in the pleurisy with effusion group suggested significant change but was based on too few cases.

Oxygen uptake in each group, despite anatomic and histologic differences, appeared to lie within the same range of improvement (8 to 10 per cent). It appeared that ventilatory function (vital capacity and minute ventilation) was most markedly improved in the pleurisy with effusion group.

DISCUSSION

The results obtained by decortication of the lung after hemothorax, particularly of short duration, indicate excellent return of pulmonary function (4). Similar results, although quantitatively decreased, occur after decortication in the more chronic forms of hemothorax. The possibility of obtaining a similar improvement in ventilatory function and oxygen uptake through decortication of the lung in pulmonary tuberculosis, in addition to the invaluable factor of

closing the pleural space, was the hope of those who revived this surgical procedure during the past decade. The advent of streptomycin and other antituberculous agents also made this approach more feasible.

Data obtained by other investigators with bronchospirometric evaluations of function before and after decortication in pulmonary tuberculosis have indicated little improvement in function (1, 2, 3). Fourteen cases with pulmonary function studies have been reported by these investigators, but only four of these had bronchospirometry before and after decortication. The group represented many far advanced cases, many with bilateral active disease and with frequent associated thoracoplasty. Relatively greater improvement in ventilation than oxygen uptake on the affected side was noted following decortication in the few cases studied bronchospirometrically, indicating impairment of ventilation-perfusion relationships (2). This relation was not found in the present series, except in the pleurisy with effusion group.

The factors implicated in the failure of the decorticated lung to return to a degree of function comparable to that after hemothorax have been adequately discussed by Wright and others (1, 3). Demonstrable underlying parenchymal disease is an important factor; yet, in the present series of unexpandable lungs following pneumothorax, the disease has appeared to be predominantly unilateral and unilobar. Review of available films prior to institution of the pneumothorax has rarely shown demonstrable involvement in other lobes. A greater degree of improvement in function might be expected on that basis. However, wider experience with planigraphy as well as findings by palpation of the entire lung by the surgeon during thoracotomy have given repeated demonstrations of the often extensive involvement of portions of the lung which appear uninvolved on the usual posterior-anterior film. In the one case in the present series (D. H.) in which early decortication was performed for a tuberculous pyopneumothorax without parenchymal or pleural disease, the procedure resulted in return of function approximating that of recent hemothorax with decortication. Failure to improve lung function following decortication may well represent changes due to underlying disease.

Bruce (5) and Pinner, Leiner, and Zavod (6) have indicated the close correlation between reduction of function and the degree of pleural exudation, fibrinothorax, and immobility of the diaphragm. Although every effort was made to free the diaphragm at decortication in the present series, no consistent degree of improvement in mobility was noted (table 1), and there was no correlation between such improvement and improvement in pulmonary function.

The 4 cases of pleurisy with effusion in the present series also demonstrate the effect upon ventilation-perfusion relationships of tuberculous disease. Despite an appreciable improvement in vital capacity, the improvement in oxygen uptake lies in the same range as the pneumothorax group. The single case of decortication following pleurisy with effusion with pulmonary function studies reported by Carroll and associates (2) had bronchospirometric studies only postoperatively, and they revealed a marked reduction in vital capacity and oxygen uptake but a normal ventilation fraction.

SUMMARY

Bronchospirometric studies before and after decortication in 9 patients with unexpandable lung following artificial pneumothorax for the treatment of pulmonary tuberculosis revealed a greater degree of improvement in oxygen uptake than in ventilatory function on the affected side.

Similar studies in 4 patients with pleural involvement secondary to tuberculous pleurisy with effusion revealed a greater increase in ventilatory function than was present in the pneumothorax group, although oxygen uptake in each group was within the same range (8 to 10 per cent).

Decortication in pulmonary tuberculosis does not offer the degree of improvement in pulmonary function often noted after decortication in nontuberculous disease and should not be the primary object of such surgery in tuberculosis.

The lack of improvement in pulmonary function after decortication may be inherent in the nature and tissue changes of tuberculous pleuropulmonary disease. Lung compression or collapse and the duration of such effects, as seen in hemothorax and other nontuberculous pulmonary involvement, may be factors of equal significance in limiting the return to normal function.

SUMARIO

Estudio Broncoespirométrico de la Función Pulmonar Consecutivamente a la Decorticación en la Tuberculosis Pulmonar

Los estudios broncoespirométricos verificados antes y después de la decorticación en 9 enfermos con pulmón inexpandible consecutivamente al neumotórax terapéutico aplicado en la tuberculosis pulmonar reveló mayor mejoramiento de la toma de oxígeno que de la función ventiladora del lado afectado.

Los estudios semejantes ejecutados en 4 enfermos con invasión pleural secundaria a pleuresía tuberculosa con derrame reveló un aumento mayor de la función ventiladora que en el grupo del neumotórax, aunque la toma de oxígeno quedó dentro de los mismos límites en ambos grupos (8 a 10 por ciento).

La decorticación no ofrece en la tuberculosis pulmonar la misma mejoría de la función pulmonar observada a menudo cuando se practica en afecciones no tuberculosas, por lo cual no debe ser la meta primaria en aquella enfermedad.

La falta de mejoría de la función pulmonar notada después de la decorticación puede formar parte inherente de la naturaleza y alteraciones histológicas de la afección pleuropulmonar tuberculosa. La compresión o colapso del pulmón y la duración de estos efectos, según se observan en el hemotórax y otros fenómenos pulmonares no tuberculosos, pueden constituir factores de igual importancia en la limitación del retorno de la función normal.

RESUME

Une étude bronchospirométrique de la fonction pulmonaire après décortication, dans la tuberculose pulmonaire

Les études bronchospirométriques pratiquées avant et après la décortication, chez 9 malades privés d'expansion du poumon à la suite de l'instauration d'un pneumothorax artificiel, pour traitement d'une tuberculose pulmonaire, ont révélé que le degré d'amélioration de la consommation d'oxygène était supérieur à celui de la fonction de ventilation du côté affecté.

Des études similaires, chez 4 malades présentant des lésions pleurales secondaires à une pleurésie tuberculeuse avec épanchement, ont montré un accroissement de la fonction de

ventilation supérieur à celui observé dans le groupe à pneumothorax, bien que la consommation d'oxygène dans chacun des groupes ait été du même ordre (8 à 10%).

Dans la tuberculose pulmonaire, la décortication ne procure pas le degré d'amélioration de la fonction pulmonaire souvent observé après la décortication dans les affections non tuberculeuses; la fonction pulmonaire ne saurait constituer l'objet initial d'une telle chirurgie dans la tuberculose.

Il est possible que le défaut d'amélioration de la fonction pulmonaire après décortication soit inhérent à la nature et aux altérations tissulaires de l'affection pleuro-pulmonaire tuberculeuse. La compression ou le collapsus du poumon et la durée de leur action, comme on l'observe dans l'hémothorax ou autres accidents pulmonaires d'origine non tuberculeuse, peuvent représenter des facteurs de valeur égale en limitant le retour à la fonction normale.

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CLOSED DRAINAGE AND THORACOPLASTY IN THE TREATMENT OF TUBERCULOUS EMPYEMA[1, 2]

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Tuberculous empyema is a grave complication of pulmonary tuberculosis, as attested by its high mortality rate. Alexander (1), collecting the results in 779 patients included in nineteen articles, found a case fatality rate of 41.6 per cent. Packard, Hayes, and Blanchet (5) corroborated this figure with the finding of a mortality of 42 per cent among 154 patients. A mixed infection reputedly carries a poorer prognosis than a simple tuberculous empyema. Leaver and Hardway (4) found a 70.9 per cent mortality in 24 cases of mixed infection, while 22.9 per cent of 35 patients died of a purely tuberculous one. Connolly and Forsee (2) reported 4 deaths among 15 cases of mixed infection and none among 7 with simple tuberculous empyema, all treated surgically. Their over-all mortality rate was 18 per cent. This represents a significant lowering of mortality, which was aided by both thoracoplasty and streptomycin. The futility of conservative treatment is well known; Cuthbert (3) showed a mortality of 81.1 per cent with such conservative care. The effectiveness of surgery would seem to depend to a large extent on the avoidance of delay in adopting operation.

It is not the purpose of the present writers to describe any new methods or techniques, but to consider a program whereby the treatment of tuberculous empyema might be better systematized. A few selected cases will be presented from a group of 15 patients operated upon. Ten of these were from the Tuberculosis Service of the Alexandria Veterans Administration Hospital during 1948 to 1950, and 5 additional cases were from private files.

The cases are generally divided into three categories: patients in the first group received only a thoracoplasty; in the second, a thoracoplasty with decortication; and the patients in the third group had a thoracoplasty with some type of Schede unroofing. All had preliminary tube drainage. A fourth group is considered wherein decortication alone was used, but no examples of this type of case are presented. Emphasis is laid on the proper timing of various operative procedures, as it is believed that this has a strong bearing on the outcome.

OBSERVATIONS

Group I, which is composed of patients treated with thoracoplasty alone, consisted of 9 patients, 8 of whom had purely tuberculous empyemata. Following intercostal drainage, partial lung expansion was obtained in 8 instances; while in the remaining patient the lung expanded completely. Preoperatively, 8 had

[1] From the Surgical Service, Veterans Administration Hospital, Alexandria, Louisiana.

[2] Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

sputum positive for acid-fast bacilli. All underwent thoracoplasty without incident, receiving streptomycin concurrently. Follow-up studies revealed that one patient developed a bronchopleural fistula one year after surgery, for which pneumonectomy was advised at another hospital. One other patient had a persistently active contralateral lesion despite an additional small thoracoplasty on that side. The disease of the other 7 patients has become inactive. These patients have returned to light or moderate work. Two cases, illustrative of this group, follow.

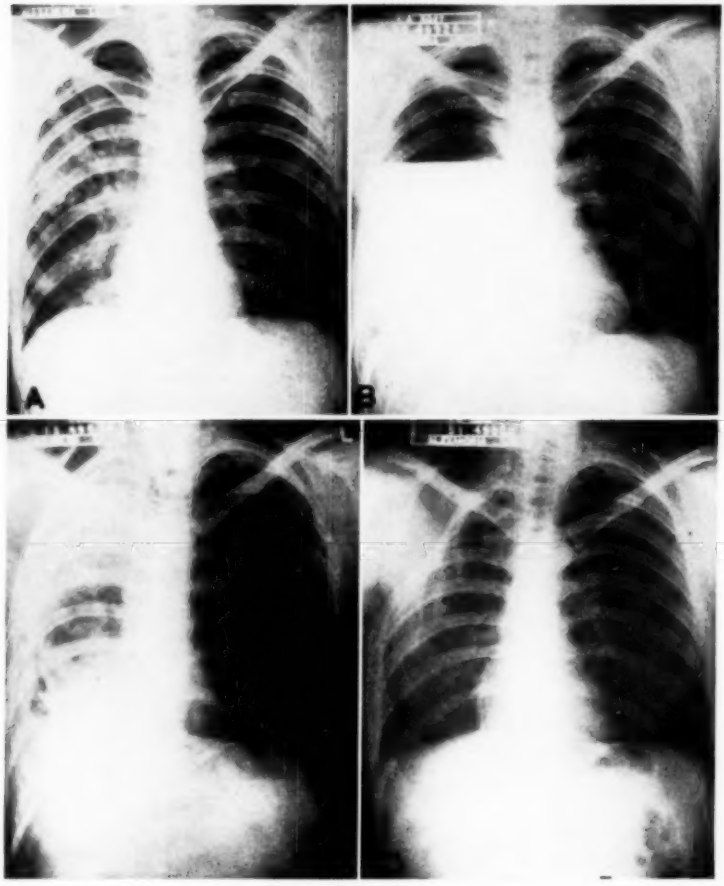
Case 1. H. W., a 27-year-old white male, was admitted to the hospital on January 28, 1949, with seven months' history of pulmonary tuberculosis. His sputum was positive for acid-fast bacilli, and an admission roentgenogram showed "honeycombing" and extensive infiltration in the right subclavicular region, with a left hilar spread of disease. Right pneumothorax was initiated on February 8 and a pneumonolysis performed on March 2. On June 30, 1949, fluid began to appear in the right pleural cavity. This was accompanied by low-grade fever, and a culture of the aspirate was positive for *M. tuberculosis*. On August 22, drainage through the right fifth interspace was performed. Expansion of the lung was slow but complete, the catheter being removed before surgery. A two-stage, five-rib thoracoplasty was begun on November 17, 1949. Streptomycin was also initiated in doses of 1 gm. daily. The sputum became negative for tubercle bacilli after the first stage of thoracoplasty. The patient was discharged from the hospital following his second and last stage of thoracoplasty and has returned to light work. Follow-up roentgenograms show minimal pleural thickening at the right base without evidence of parenchymal disease. A study of illustrative films shows the extent of the original parenchymal involvement requiring permanent collapse (figures 1*A*, *B*, *C*, and *D*).

Case 2. R. W., a 36-year-old white male, was first seen by one of the writers (L. F. K.) in September, 1947. He had a two-year history of pulmonary tuberculosis which mainly involved the left lung. He developed a spontaneous pneumothorax on the left early in 1947 which became complicated by a mixed empyema. The bronchopleural fistula closed, but the empyema persisted. The patient showed evidences of disease toxicity with daily temperature elevations to 104°F. Roentgenograms at this time showed 80 per cent collapse of the left lung by fluid. On October 24, 1947, left intercostal drainage was done with evacuation of large amounts of tuberculous pus. He was treated intensively with streptomycin, 1 gm. daily, and supportive measures, with consequent improvement. Repeated roentgenograms at this time showed 50 per cent collapse of the lung, with parenchymal disease limited to the upper lobe. A three-stage, nine-rib thoracoplasty was started on November 29, 1947. The intercostal catheter was removed after the last stage, and the sputum became negative for tubercle bacilli after the second stage. The patient eventually returned to work as a lumber mill operator, and his disease has remained healed.

Group II comprises 4 patients who, in addition to thoracoplasty, were subjected to decortication. All had purely tuberculous empyemata and sputum positive for acid-fast bacilli. In 3 of these patients the sputum was converted by operation, and in one it remained intermittently positive for tubercle bacilli. All had uneventful courses except one who suffered severe toxicity when a bronchopleural fistula reopened. This case will be discussed in detail. All patients in this group have left the hospital and have remained well. Two illustrative case reports are as follows.

Case 3. H. P., a 23-year-old white male, was admitted to the hospital on July 26, 1950, with a two-year history of pulmonary tuberculosis. Right pneumothorax had been initiated and

continued since October, 1948. One month prior to admission, fluid began to appear in his right pleural cavity. On admission, this fluid was aspirated, cultured, and found to be positive for *M. tuberculosis* although his sputum was negative for tubercle bacilli. A roent-



Case 1 (H. W.)

FIG. 1 *A*. Admission roentgenogram. *B*. Roentgenogram showing empyema. *C*. Roentgenogram showing expansion with tube drainage. *D*. Roentgenogram taken after thoracoplasty.

genogram at this time showed a 90 per cent collapse of the right lung by fluid and air. Attempts to effect re-expansion by repeated aspirations and pneumoperitoneum failed. Consequently, on November 10, 1950, catheter drainage through the right fifth interspace was

carried out. On November 27, 1950, the patient began to complain of severe pain in the right hemithorax. He rapidly became toxic with daily temperature elevations to 103.6°F. It was noted that the fluid which drained from the catheter became somewhat thicker; however, no organism other than *M. tuberculosis* was found on culture. Reopening of the bronchopleural fistula was apparent from continued bubbling into the water trap. Accordingly, the patient was given streptomycin, 1 gm. daily parenterally, and both penicillin and streptomycin were instilled daily into the pleural space. Intensive supportive therapy in the form of transfusions was also employed. His general condition improved and his temperature fell slowly. Repeated roentgenograms showed complete failure of lung expansion. Therefore, a first-stage thoracoplasty was done on December 29, 1950, followed by a second-stage thoracoplasty and decortication of the lower lobe on January 19, 1951. Recovery was uneventful, and the tube was removed one week later, with rapid closing of the sinus tract. He was discharged from the hospital on July 6, 1951. Roentgenograms just prior to discharge revealed a small amount of residual thickening at the right base which, on serial studies, had been diminishing. A perusal of illustrative films shows extensive parietal "peel" requiring decortication of the lower right lung (figures 2 *A*, *B*, *C*, and *D*).

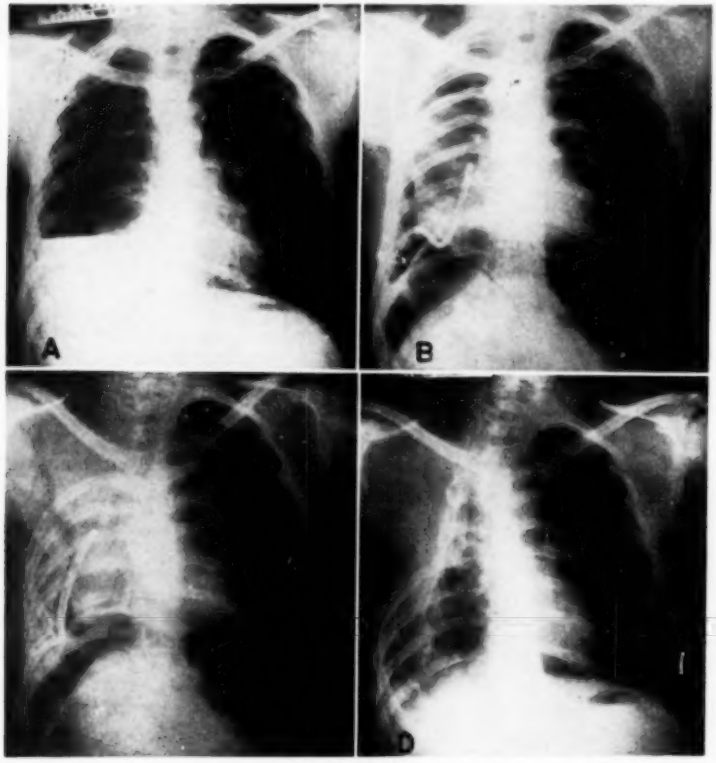
Case 4. E. B., a 28-year-old white male, was admitted to the hospital for the third time on August 8, 1949, with a three-year history of pulmonary tuberculosis. The disease was found in 1946 during a routine survey by the state board of health. Right pneumothorax was initiated in 1946 and a pneumonolysis was done. The patient developed fluid in the right pleural cavity in March, 1947, and was treated by repeated aspirations. Culture of the aspirate in July, 1949, was positive for *M. tuberculosis*. A roentgenogram on admission showed fluid and thickened pleura completely surrounding the right lung, with a 70 per cent collapse of the lung. On August 16, 1949, catheter drainage was done through the right fourth interspace, but no lung expansion was obtained. At this time, the patient was also started on streptomycin, 1 gm. daily. A two-stage, seven-rib thoracoplasty was started on August 31 and did not adequately obliterate the empyema cavity. Therefore, on November 11, 1949, decortication of the middle and lower lobes was performed. The catheter was removed on December 9, and subsequent roentgenograms revealed good space closure.

The patient was discharged from the hospital two months later with a small residual draining sinus. He was readmitted to the hospital several months later, at which time the sinus tract was excised and found to have been confined to the subscapular space. Excision was repeated three times in an effort to close the sinus, but each time it reopened. Silk sutures were believed to be responsible. The patient left the hospital and still has a residual sinus at this time despite the fact that the empyema is apparently cured.

Group III was composed of 2 patients, both of whom had a final Schede stage in addition to the conventional thoracoplasty. Both had sputum negative for tubercle bacilli preoperatively. In both, the procedure was effective in curing the empyema although one patient died from myocardial infarction nine months following his discharge from the hospital. A brief description of one of these cases follows.

Case 5. C. L., a 22-year-old white male, was admitted to the hospital on April 19, 1947, with a history of sudden pulmonary hemorrhage one week prior to admission. Initial roentgenograms revealed exudative tuberculous disease in the left mid-lung field. His sputum was repeatedly negative for tubercle bacilli. A left pneumothorax was started on April 26, 1947. Three months later, fluid was present in the left pleural cavity, with a spread of the disease to the right lung. Repeated aspirations were necessary to relieve dyspnea. *M. tuberculosis* was cultured from the fluid on March 10. On December 26, 1948, catheter drainage through the left sixth rib was instituted and suction applied. The patient remained mildly toxic, and the lung failed to expand. Streptomycin therapy was initiated at this time in doses of

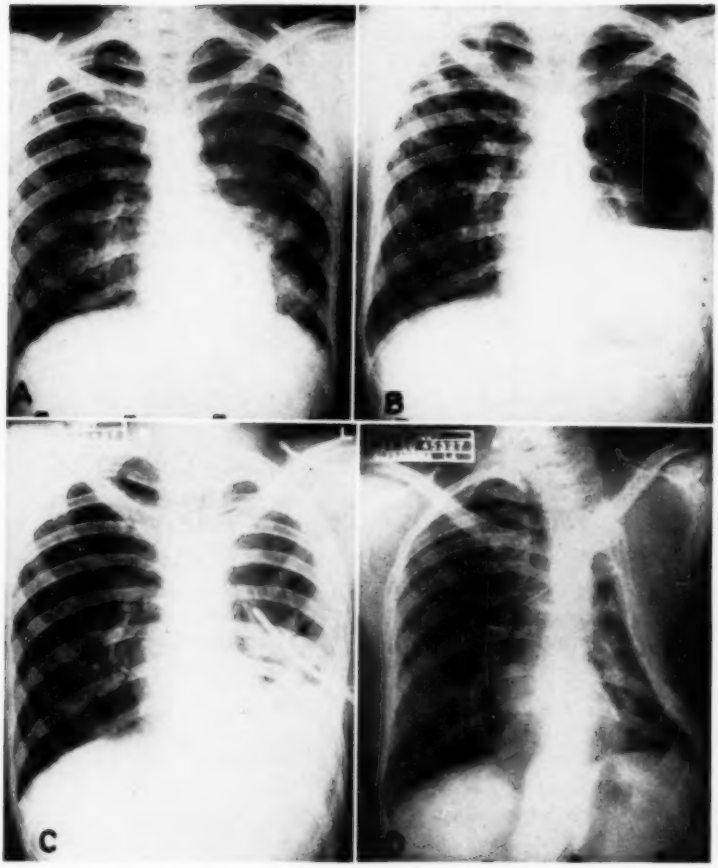
1 gm. daily. Two months later a two-stage, seven-rib thoracoplasty was begun, the patient receiving streptomycin concurrently. This treatment was insufficient to obliterate the cavity, however, and a partial Schede unroofing with decortication of the residual space became necessary on October 14, 1949. The empyema space at the time of surgery was 7.5 by 5 by 5 cm. in size. The catheter was removed six days later, and the sinus tract



Case 3 (H. P.)

FIG. 2 *A*. Admission roentgenogram. *B*. Roentgenogram showing poor expansion on drainage. *C*. Roentgenogram taken when thoracoplasty was partly completed. *D*. Roentgenogram taken after decortication and thoracoplasty were completed.

healed promptly. He left the hospital three months after his last operation. Two months later he returned to have three persistent tuberculous sinuses excised from the scar. Roentgenograms of the chest at present writing, twenty months after discharge, show his disease to be inactive. Clinically, his wound remains healed. A review of illustrative films shows poor expansion following tube drainage and the satisfactory final result (figures *3 A*, *B*, *C*, and *D*).



Case 5 (C. L.)

FIG. 3. *A*. Admission roentgenogram. *B*. Roentgenogram showing left empyema and right lung spread. *C*. Roentgenogram taken after tube drainage. *D*. Roentgenogram taken after thoracoplasty and unroofing were completed.

DISCUSSION

Although it is not specifically publicized, most thoracic surgeons formulate a definite policy for the management of these cases. Conservative treatment has been practically abandoned because of its almost hopeless results. Treatment is designed to eradicate the infection with the least radical method which will

obliterate the empyema space; to provide necessary collapse to underlying unstable parenchymal disease; and to afford good functioning remaining lung tissue which is unhindered by surrounding pleural "peel." Inasmuch as empyema, simple or mixed, is such a devastating affliction with its toxic effects, many corollary measures must be taken along with definitive surgery to promote and recover a better state of health in these chronically ill patients.

Once the diagnosis of tuberculous empyema has been made, further aspirations are terminated owing to the tendency of this practice to result in multiple chest wall sinuses. The writers have seen cases wherein the sinus formation compromised an otherwise simple thoracoplasty incision. Although cultures of the material are made, the results of culture are not awaited before institution of the program. The toxicity of the patient with turbid fluid in the aspirate is sufficient to necessitate active measures. The writers do not believe that any complete agreement among surgeons can be obtained on what constitutes empyema. Ordinarily, it would be anticipated that the fluid would show strains of tubercle bacilli and other bacteria on culture, but many empyemata are sterile on culture. This finding should not influence judgment and lead to omission of the necessary treatment to a toxic patient.

All of the patients in the present series received closed drainage, which should be done preferably by the intercostal route. The tube is placed anteriorly in a segment of the thorax which will not be disturbed until the last thoracoplasty stage. Early tube drainage is paramount for many reasons:

> (*1*) It provides continuous and fairly complete exit for the purulent products of the disease, thereby reducing toxicity; (*2*) by early expansion of the lung, further pleural thickening is minimized; (*3*) extension of pus to other thoracic compartments is avoided; and (*4*) dyspnea in many cases is alleviated.

The writers have seen this simple measure of continuous drainage improve the well-being of the patient so significantly that weight gain soon became apparent.

Streptomycin therapy was given 11 of the 15 patients in the present series. For the most part, the drug was administered at the time of tube drainage and continued for various periods of time, as indicated by table 1. The regimen for this drug changed frequently during the course of study, and at present writing streptomycin is being given in 1 gm. doses twice weekly.

Repeated blood transfusions are usually necessary for these patients. Erythrocyte and hemoglobin deficits must be kept corrected. Moreover, these patients will show protein loss. The protein losses are more apparent when the amounts of exudates lost from tube drainage are subject to analysis. Such protein deficits may be made up by supplementary protein in the diet.

As a rule, the writers have not attempted to sterilize the remaining space with detergents or germicides. It is not believed that such a program affords significant results when the empyema space is large. Antimicrobial drugs may be instilled, but even this procedure is usually deferred until surgical measures have been taken to reduce the space to a minimum. Streptomycin or para-aminosalicylic acid instillations are relatively ineffective when there is a voluminous surface area

and a large quantity of pus. Parenteral streptomycin is considered for patients with active homolateral or contralateral lesions. In stable cases, it is better to defer streptomycin until the patient is ready for decortication or resection.

Mild suction is applied to the endothoracic drainage when the patient's toxic symptoms abate. To apply suction prematurely may make the patient sicker than previously and may reopen a bronchopleural fistula. When used by the present writers, the suction has been mild (15 cm. of water) and intermittent, utilizing the thermotic type of apparatus. This adjunct may be successful in reducing the size of the empyema space and, if the pleural "peel" is not great, may even succeed in closing the space in a few cases. Needless to say, a patient with a small or no empyema space is a better-risk patient than one with a large one.

In reparative measures, the choice of procedure is dependent on the amount and type of parenchymal disease, amount and location of the pleural "peel," presence of a bronchopleural fistula, and the progress of the patient after surgical measures have begun. The time to institute definitive surgery has been a moot point with some surgeons. It is significant that 9 of the 15 patients of the present series underwent the first stage of thoracoplasty within ten days of the intercostal drainage. If the patient's general condition is satisfactory, e.g., if he is afebrile, his erythrocyte count approximates normal, his protein and fluid losses remedied, and appetite good, it is believed that the surgical program should be started. The sooner the empyema space is reduced, the better the outlook for the patient. Continued delays only lead to a continued toxic state, with eventual development of amyloid disease and other cardiorenal disease.

Patients with sufficient lung disease to demand permanent collapse before the onset of empyema should be evaluated seriously for permanent collapse at this time. Even though a previous pneumothorax has appeared to control the parenchymal disease of the lung, it is the writers' belief that such patients might have had sufficient disease to have warranted a thorocoplasty initially. Many of the effusions and empyemas following pneumothorax can be laid to excessive extents of pulmonary disease treated by this measure. Such a patient is then subjected to a staged conventional thoracoplasty, care being taken not to expose the tube drainage tract until the last stage. The number of ribs removed usually coincides with the extent of previous pulmonary disease. A careful study of the amount of remaining "peel" and space should be made before performance of the last stage. If either are significantly great, preference should be given to other types of surgery discussed below. This will depend on leaving the functioning efficient lung which is free from parenchymal disease.

Consideration should be given the question of removal or retention of the drainage tube between all stages. If the space obliterates before the thoracoplasty is completed, the tube can be removed. It is important to be sure that no residuum of space is left, for a small nidus can redevelop into a large "recurrent" empyema. Any space which will hold an amount of saline greater than the tube capacity is still a space, and tubes must be retained until such a space is obliterated.

Patients who do not show significant amounts of pulmonary disease from the onset can be subjected to decortication without thorocoplasty. It is not believed

TABLE 1

BACTERIOLOGIC RESULTS OF TREATMENT

CASE	STREPTOMYCIN 1 GM. DAILY	SPUTUM PREOPERATIVELY	SPUTUM POSTOPERATIVELY	SPUTUM POST STREPTOMYCIN	REMARKS
	days				
R. G.	76	Positive for *M. tuberculosis*	Negative for *M. tuberculosis* (concentrated) 1 month	Negative for *M. tuberculosis* (concentrated) 1 month	Left against advice in two months; no follow-up.
A. H.	40	Positive for *M. tuberculosis*	Negative for *M. tuberculosis* (concentrated) 6 months	Negative for *M. tuberculosis* (concentrated) 6 months	Bronchopleural fistula reopened after two years; sputum again positive for *M. tuberculosis*.
E. H.	42	Positive for *M. tuberculosis*	Positive for *M. tuberculosis*	Positive for *M. tuberculosis*	Active contralateral lesion; empyema cured.
C. L.	45	Negative for *M. tuberculosis*	Negative for *M. tuberculosis*	Negative for *M. tuberculosis*	Sputum remained "negative" for two years; empyema cured.
H. K.	42	Positive for *M. tuberculosis*	Positive for *M. tuberculosis*	Positive for *M. tuberculosis*	Active contralateral lesion; extrapleural plombage after two years; "negative" sputum culture two months.
H. W.	44	Positive for *M. tuberculosis*	Negative for *M. tuberculosis* (concentrated) 2 weeks	Negative for *M. tuberculosis* (concentrated) 1 week	Lesion arrested in fifteen months; empyema cured.
J. M.	90	Positive for *M. tuberculosis*	Negative for *M. tuberculosis* (concentrated) 2 months	Negative for *M. tuberculosis* (concentrated) 2 months	Left against advice after five months; no follow-up.

E. B.	74	Positive for *M. tuberculosis*	Negative for *M. tuberculosis* (concentrated) 1 month	Negative for *M. tuberculosis* (concentrated) 1 month	Reported intermittent sinus drainage after two years.
C. H.	0	Negative for *M. tuberculosis*	Negative for *M. tuberculosis*	—	Empyema well for four months; no follow-up.
H. P.	66	Negative for *M. tuberculosis*	Negative for *M. tuberculosis*	Negative for *M. tuberculosis*	Empyema well for seven months; no follow-up
R. E. C.	0	Positive for *M. tuberculosis*	Culture negative for *M. tuberculosis* 1 month	—	"Negative" for four years; empyema cured.
R. V. R.	0	Positive for *M. tuberculosis*	Culture negative for *M. tuberculosis* 1 month	—	"Negative" for four years; empyema cured.
R. W.	68	Positive for *M. tuberculosis*	Culture negative for *M. tuberculosis* 1 month	Culture negative for *M. tuberculosis* 1 month	"Negative" for four years; empyema cured.
C. H. B.	98	Positive for *M. tuberculosis*	Culture negative for *M. tuberculosis* 2 weeks	Culture negative for *M. tuberculosis* 2 months	"Negative" for four years; empyema cured.
S. H.	0	Negative for *M. tuberculosis*	Negative for *M. tuberculosis*	—	Died nine months later of myocardial infarction; empyema cured.

that this type of case is common, but it does occur. Such decortication need not involve removal of the thickened pleural cap overlying previous upper lobe disease. The writers are in agreement with others that this particular "peel" acts as an effective endocostal collapse for such a lung, and the removal of this portion of the membrane may open old tuberculous foci. Thus, only the useful portions of the lung are decorticated. Decortication is also employed as a last stage in patients who undergo thoracoplasty and in whom there is sufficient parietal and visceral encasement to compromise the function of the underlying otherwise healthy lung. There are few measures more unphysiologic than eradicating an empyema successfully and leaving a large portion of the lung collapsed and airless because of an encompassing pleural capsule. The inefficiency of a lung under pleural thickening is well recognized. Such a lung may be quite useful and necessary to a patient should he develop contralateral spread of disease, not to mention the reduction of breathing reserve should he return to active life.

Patients who show persistent space infections after conventional thoracoplasty and in whom decortication has been ineffectual must come to a limited Schede type of unroofing. Underlying fibrotic lung and bronchopleural fistula are most often the reason for failure of the decortication. The writers have seen patients in whom decortication was not technically possible in whom repeated attempts led to tearing of large areas of fibrotic lung. Removal of the tube at this last stage and excision of the parietal wall of the remaining empyema will lead to final eradication. All portions of the rib cage over the space are removed down to the visceral pleura, but the intercostal bundles and chest wall muscles are salvaged. If a bronchopleural fistula is present, one of the muscle bundles should be sutured firmly against it. Other muscles are allowed to fall against the lung after thoroughly debriding the visceral surface of all soft granulations. Some temporary drainage is required to release blood and serum for a few days. Catgut suture is advocated for all deep structures, as it is believed that many of the sinus formations were the result of nonabsorbable materials.

Since the advent of streptokinase-streptodornase, a few small spaces have been salvaged without performance of a Schede operation. These enzymes are utilized extensively when it is believed that the parenchymal portion of the lung has been well collapsed. The writers are unable to formulate any strict policy on what to expect from the use of enzymes at this time but recommend that they be tried in relatively small-space infections. Enzymatic treatment should not replace the active surgical part of the program, as other writers have repeatedly emphasized. The greatest usefulness of the enzymes may lie in the closure of sinus tracts which are not easily amenable to excision.

There remains a small group of patients with bronchopleural fistula in whom nothing short of pulmonary resection will effect a cure of the empyema. Such cases exhibit destroyed lung in either a lobe or an entire lung. The effectiveness of pneumonectomy in attaining bronchial closure is dependent on the elimination of as much surrounding infection as possible. Extrapleural types of resection are advocated, therefore, to remove the thick infected scar around the hilum. Whenever this is not possible, the rate of fistula recurrence is apt to be high, as a space

remains which bathes the bronchial closure with infected exudate. Failure in such cases is even more manifest in patients with streptomycin-resistant infections. It remains then for Eloesser flap drainage and myoplasty to close such a case. The ever present chance of contralateral spread of disease often delays a well-meant surgical program. This type of case, while in the minority, remains a difficult problem.

SUMMARY

A program is formulated for the management of tuberculous empyema. The treatment is, in the main, surgical, and consists of tube drainage supplemented by thoracoplasty and/or decortication, depending on the nature of the lesions in the underlying lung.

Several illustrative examples of a group of 15 cases are presented. Of these, all but 3 patients are well, with sputum negative for *M. tuberculosis*, and only one has a residual chest wall sinus.

SUMARIO

El Drenaje Cerrado y la Toracoplastia en el Tratamiento del Empiema Tuberculoso

Formúlase un plan para la asistencia del empiema tuberculoso. El tratamiento es, en lo esencial, quirúrgico, consistiendo en drenaje con sonda, complementado con la toracoplastia y/o la decorticación, conforme a la naturaleza de las lesiones en el pulmón subyacente.

Preséntanse varios ejemplos típicos de un grupo de 15 casos. De ellos, todos, menos 3, están bien, con esputo negativo para el *M. tuberculosis*, y únicamente uno tiene una fístula residual de la pared torácica.

RESUME

Drainage fermé et thoracoplastie dans le traitement de l'empyème tuberculeux

Présentation d'un programme de traitement de l'empyème tuberculeux. Le traitement est surtout d'ordre chirurgical et consiste en drainage complété par la thoracoplastie ou la décortication, ou par l'un et l'autre de ces procédés, selon la nature des lésions du poumon sous-jacent.

Plusieurs exemples illustrant ce programme sont fournis par un groupe de quinze cas. Parmi ceux-ci, tous sauf 3, ont des crachats négatifs pour le *M. tuberculosis* et un seul conserve une fistule résiduelle de la paroi thoracique.

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COMBINED DAILY TERRAMYCIN AND INTERMITTENT STREPTOMYCIN IN THE TREATMENT OF PULMONARY TUBERCULOSIS[1,2]

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INTRODUCTION

With the knowledge that terramycin exerts *in vitro* and *in vivo* antituberculous activity (1, 2, 3, 4), a pilot study using terramycin, alone and in combination with streptomycin, for the treatment of pulmonary tuberculosis was carried out at Fitzsimons Army Hospital during 1950 (5). Because the study suggested that terramycin, like para-aminosalicylic acid, may delay the emergence of bacterial resistance to streptomycin, further trial with this drug in the treatment of tuberculosis seemed justified.

METHOD OF STUDY

Seventy patients with active pulmonary tuberculosis were selected by a process of randomization from patients meeting the following criteria: (*1*) no previous antituberculous drug therapy, (*2*) bacteriologically proved disease (by culture), and (*3*) disease of greater than minimal extent. Sixty-six patients received 5 gm. of terramycin hydrochloride daily (1.25 gm. orally, four times a day) and 2 gm. of streptomycin sulfate every third day (1 gm. intramuscularly, twice a day), both drugs for a period of 120 days. Because 4 patients did not receive this amount of terramycin, they were not included in the statistical analyses and will be commented on later. During the period of observation, the patients were on a strict rest regimen.

EVALUATION

The series of 66 patients consisted of 62 men and 4 women, of whom 25 (37.9 per cent) had far advanced, and 41 (62.1 per cent) had moderately advanced, disease. Each patient's tuberculous lesion was classified by taking into consideration serial chest roentgenograms and known duration of disease as follows: new, resolving lesions (5 cases); new, poorly resolving lesions (1 case); new, mixed, resolving and poorly resolving lesions (36 cases); old lesions (4 cases); and mixed, new, and old lesions (20 cases) (table 1).

The patients were evaluated clinically, roentgenographically, and bacteriologically, and the toxic manifestations were recorded.

[1] From the Pulmonary Disease Service and the Research and Development Branch, Fitzsimons Army Hospital, Denver 8, Colorado.

[2] The terramycin hydrochloride used in this study was kindly supplied through the courtesy of Charles Pfizer & Co., Inc., Brooklyn, New York.

Clinical: Clinical evaluation included significant change in cough, sputum volume, and weight, comparing the findings at the start of therapy with those on the one hundred twentieth day (figure 1). Cough was graded as slight, moderate, or severe.

Of the 58 patients (87.9 per cent) who had cough at the onset of drug treatment, 29 (50.0 per cent) had improvement, 28 (48.3 per cent) were unchanged, and one (1.7 per cent) had become worse after 120 days.

A sputum volume of 10 cc. or greater per day and a 10 cc. or greater volume change during treatment were considered significant and used as criteria for the evaluation. Of the total number of patients, 44 (66.6 per cent) had a daily sputum volume of 10 cc. or greater per day at the beginning of drug therapy. Of these, 26 (59.1 per cent) had a reduction, 2 (4.5 per cent) had an increase, and 16 (36.4 per cent) had no essential change in sputum volume after 120 days of therapy.

TABLE 1

CLINICAL PATHOLOGIC TYPE OF DISEASE

TYPE OF LESION	PATIENTS	
	Number	Per cent
New lesions		
Resolving (exudative)	5	7.6
Poorly resolving (caseous)	1	1.5
Mixed, new lesions	36	54.5
Old lesions (fibrocaseous)	4	6.1
Mixed, new, and old lesions	20	30.3
Total	66	100.0

A weight gain or loss greater than five pounds was considered significant. Of the 66 patients who received the drugs for a total of 120 days, 31 (47.0 per cent) had weight gain, 13 (19.7 per cent) had weight loss, and 22 (33.3 per cent) had no change.

Roentgenographic: Roentgenographic trend and treatment response were evaluated by a panel of five physicians on a five-point scale as follows: *marked improvement, moderate improvement, slight improvement, no change,* and *worsening* (figure 2). The presence of cavities and their response during therapy were not considered in arriving at the degree of roentgenographic change. Fifty-four (81.8 per cent) of the patients had disease which was stable as determined by pretreatment films. By the same criterion, 5 (7.6 per cent) had regressive, and 7 (10.6 per cent) had progressive, disease.

By comparing the chest films taken on the first and one hundred twentieth days of treatment, one patient (1.5 per cent) had marked roentgenographic improvement, 32 (48.5 per cent) had moderate improvement, 31 (47.0 per cent) had slight improvement, 2 (3.0 per cent) had no change, and none (0 per cent) became worse. At the beginning of drug therapy, 38 patients (57.6 per cent) had

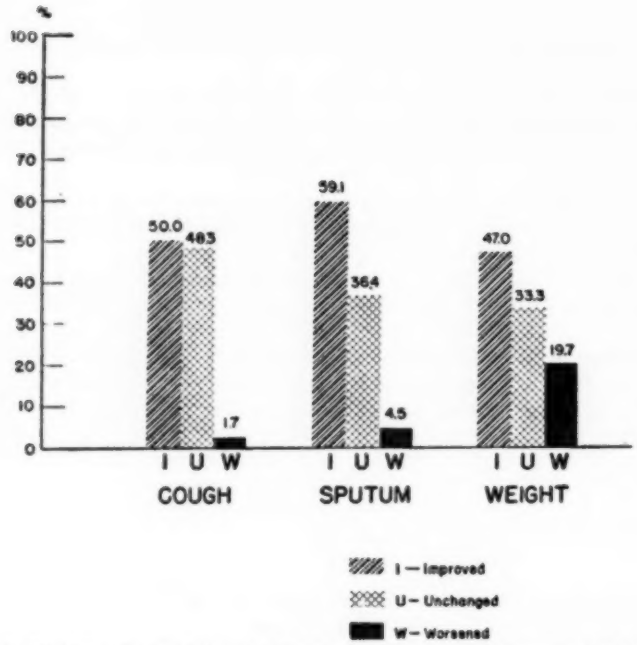

FIG. 1. Clinical response of 66 patients treated with streptomycin every third day and terramycin every day.

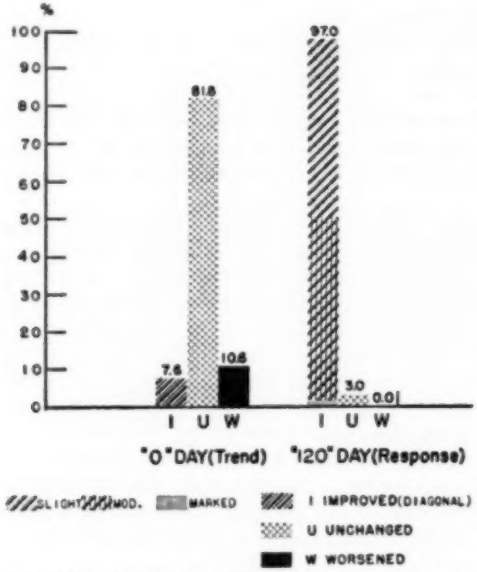

FIG. 2. Roentgenographic trend and treatment response in 66 patients treated with streptomycin every third day and terramycin every day.

demonstrable cavities on postero-anterior or apical films. After 120 days of drug therapy, the cavity was lost to view in 4 patients (10.5 per cent).

Bacteriologic: Sputum or fasting gastric specimens were examined at two-week intervals, using conventional smear and culture techniques. Cultures showing no growth after seven weeks' incubation were discarded as negative. Drug-sensitivity studies were performed on all positive cultures,using modified Herrold's egg-yolk agar containing 0, 1, 10, and 100 γ of streptomycin per ml., and on oleic-acid-albumin agar containing 0, 6, 12, 25, 50, 100, and 200 γ of terramycin per ml. After seven to fourteen days of incubation, growth on the drug-containing medium was evaluated by comparison with the control. In accord with previous studies from this hospital, cultures showing growth in the presence of 10 γ of streptomycin and 50 γ of terramycin per ml. equal to that on the control were arbitrarily called "resistant."

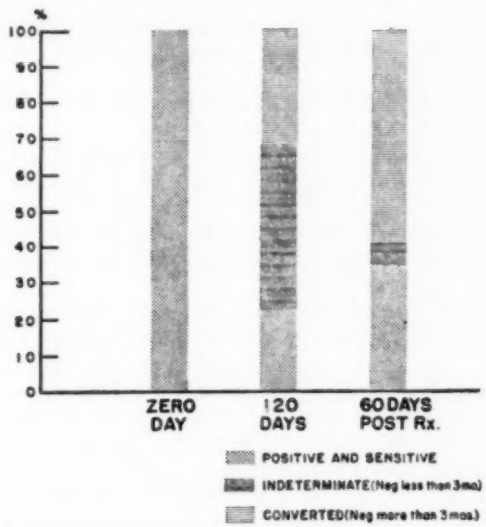

FIG. 3. Bacteriologic response in 66 patients treated with streptomycin every third day and terramycin every day.

At the onset of chemotherapy, all patients yielded positive cultures sensitive to both drugs (figure 3). At the one hundred twentieth day, sputum cultures from 51 of the 66 (77.3 per cent) patients who received the full course of treatment were negative for *M. tuberculosis*. Positive cultures obtained from the other 15 patients remained susceptible to both drugs by the criteria employed in this paper, and no definite trend toward increased bacterial resistance was observed within these limits. Sixty days after the end of therapy, cultures from 25 of the 64 patients (39.1 per cent) followed were positive for *M. tuberculosis* and the bacilli were sensitive to both agents. The only instance of bacterial resistance encountered in this study was seen in one of the 4 patients unable to tolerate the full amount of terramycin for the entire 120 days. After three months

of drug therapy, cultures of tubercle bacilli from this patient were resistant to 100 γ of streptomycin per ml. but remained susceptible to terramycin.

Drug toxicity: Complete studies for renal, hepatic, and eighth cranial nerve toxicity were not performed in this evaluation in view of the fact that detailed investigation of these systems in the pilot study previously carried out at this hospital showed no abnormality (5). The evaluations which were directed toward these systems in this study were nonrevealing. Skin lesions, evidence of avitaminosis, and hematologic abnormalities were not observed. While all of the 27 patients who received 7 gm. of terramycin daily in the pilot study experienced either anorexia, nausea, vomiting, diarrhea, or combinations of these symptoms, only 70 per cent of the patients in this study who received 5 gm. of terramycin daily have shown symptoms of this type. The majority manifested symptoms immediately; within 60 days, however, a large number of these same patients had become essentially symptom free except for anorexia, which persisted throughout the 120-day period.

Of the 70 patients selected for this study, 4 were not able to tolerate the full amount of terramycin for 120 days. Two of the patients, one man and one woman, were able to tolerate terramycin approximately two-thirds of the time. A third patient, a man, was able to tolerate only 3 to 4 gm. of this drug daily for the entire 120 days. The fourth patient, a woman, was able to take 5 gm. of terramycin approximately 50 per cent of the time. With the exception of these 4, every patient was able to take the full dosage schedule of terramycin (5 gm. daily) for the full treatment period.

The drug was best tolerated when taken with meals. Additional nourishment was given with the evening dose. In some of the more severe cases of gastrointestinal toxicity, corn syrup given with terramycin was found to alleviate the symptoms. Occasionally a milk and cream mixture, Dramamine, atropine, or phenobarbital were employed with good results in reducing nausea.

No definite toxicity attributable to streptomycin was encountered.

Post-treatment follow-up studies: Following the complete course of terramycin and streptomycin (120 days), 64 of the 66 patients were studied for an additional 60 days, during which time they had no further chemotherapy. Pneumoperitoneum was added in 60 of the 64 cases. Of the 2 patients lost to this 60-day follow-up, one was continued on drugs because of extent and type of disease, and the other had excisional surgery and thoracoplasty shortly after the termination of chemotherapy.

In this post-treatment period, the majority of the patients had continued favorable clinical, roentgenographic, and bacteriologic response; however, 5 patients showed clinical worsening, 5 roentgenographic worsening, and sputum from 10 patients again became positive for *M. tuberculosis.*

COMMENT

Seventy patients were studied in the evaluation of a treatment regimen consisting of terramycin and streptomycin. Four of the 70 patients were not considered in the statistical analyses because the full dosage of terramycin was not

taken. In 3 of these 4 patients the clinical, roentgenographic, and bacteriologic response was favorable. The fourth patient, who was able to take terramycin only 50 per cent of the time, also showed clinical and roentgenographic improvement, but yielded tubercle bacilli resistant to streptomycin after three months of chemotherapy.

With the exception of weight gain, the clinical improvement obtained was comparable to that observed with other combined drug regimens using streptomycin. It was believed that the weight loss was due to the anorexia noted during the period of terramycin administration.

The roentgenographic response in this relatively small series was most favorable. The degree of improvement, both the total (97.0 per cent) and the moderate and marked improvement (50 per cent), is slightly better than that seen in any of the 120-day combined drug regimens employed at Fitzsimons Army Hospital during the past four years. This is even more impressive when it is remembered that only 7.6 per cent of the patients had new, resolving lesions at the start of therapy.

The high incidence (77.3 per cent) of patients whose sputum became negative for tubercle bacilli during chemotherapy is additional evidence of the therapeutic effectiveness of this regimen. The most significant observation in this study was the lack of development of bacterial resistance to either drug in all 25 patients able to tolerate the full dosage of terramycin and from whom positive cultures could be obtained on or after the end of chemotherapy. Using the same laboratory methods and criteria, an incidence of 31 per cent bacterial resistance was encountered when 2 gm. of streptomycin was given every third day for 120 days without an adjuvant drug (6).

Although frequently irritating to the gastrointestinal tract, a dose of 5 gm. of terramycin daily can be taken by virtually all patients with a minimum of difficulty. It is believed that the degree of patient acceptance correlates well with the understanding and interest shown by the physician for his patient. A good "doctor-patient" relationship seemed to be most important in minimizing the undesirable side effects. A patient who was made to understand the seriousness of his disease and the importance of the drug therapy in his over-all treatment seemed to be better able to tolerate terramycin. This observation was made so frequently that it could not be overlooked as a significant factor.

Since pneumoperitoneum was added, it is believed that a detailed recording of the post-therapy data, other than bacterial "conversion" and sensitivity studies, would not be pertinent to the present discussion.

SUMMARY

Seventy patients with active pulmonary tuberculosis were selected for treatment for 120 days with 5 gm. of terramycin daily and 2 gm. of streptomycin every third day.

The clinical, bacteriologic, and roentgenographic responses of these patients were evaluated and the toxic manifestations discussed.

Sixty-six patients in this series tolerated 5 gm. of terramycin daily for 120

days with a minimum of difficulty. The remaining 4 patients were able to take the drug on a decreased dosage schedule.

Of the 66 patients who completed the full course of therapy, 97.0 per cent showed roentgenographic improvement of all degrees, 50 per cent showing marked or moderate improvement.

At the end of drug therapy, 77.3 per cent of the 66 patients were bacteriologically negative for *M. tuberculosis*. By National Tuberculosis Association standards, 59.4 per cent had "converted" their sputum by the end of the 60-day follow-up period.

After the end of therapy, cultures positive for *M. tuberculosis* were obtained from 25 of the patients who had completed the prescribed course of treatment. In every instance, these cultures were found to be susceptible to both streptomycin and terramycin.

SUMARIO

La Combinación de Terramicina Diaria y Estreptomicina Intermitente en el Tratamiento de la Tuberculosis Pulmonar

Setenta enfermos con tuberculosis pulmonar activa fueron escogidos para tratamiento durante ciento veinte días con 5 gm. de terramicina diariamente y 2 gm. de estreptomicina cada tres días.

Justiprécianse las respuestas clínicas, bacteriológicas y radiográficas de dichos enfermos y se discuten las manifestaciones tóxicas.

Sesenta y seis enfermos de la serie toleraron 5 gm. diarios de terramicina durante ciento veinte días con un mínimo de dificultad. Los otros 4 enfermos tomaron la droga, pero con un esquema posológico más bajo.

De los 66 sujetos que terminaron la serie terapéutica completa, 97.0 por ciento mostraron mejoría radiográfica en mayor o menor grado, y 50 por ciento pronunciada o moderada.

Al terminar la farmacoterapia, 77.3 por ciento de los 66 enfermos eran bacteriológicamente negativos para el *M. tuberculosis*. Conforme a las pautas de la Asociación Nacional contra la Tuberculosis de los E. U. A., 59.4 por ciento habían "virado" el esputo al terminar el período de sesenta días de observación subsiguiente.

Después de terminada la terapéutica, obtuviéronse cultivos positivos para el *M. tuberculosis* de 25 de los enfermos que completaron la serie de tratamiento prescrita. En todos estos casos, los cultivos resultaron ser sensibles tanto a la estreptomicina cuanto a la terramicina.

RESUME

Combinaison de l'administration quotidienne de terramycine et de l'administration intermittente de streptomycine dans le traitement de la tuberculose pulmonaire

Soixante-dix malades atteints de tuberculose pulmonaire en activité ont été sélectionnés pour un traitement de cent-vingts jours avec une dose de terramycine de 5 grammes par jour et d'une dose de streptomycine de 2 grammes tous les trois jours.

Les résultats ont été évalués du point de vue clinique, bactériologique et radiologique et les réactions d'intolérance ont été étudiées.

Soixante-six sujets de cette série ont toléré 5 grammes de terramycine par jour pendant cent-vingts jours avec un minimum de réactions. A doses décroissantes, les quatre autres malades ont bien supporté cette médication.

Parmi les 66 malades ayant reçu la série complète du traitement, l'amélioration radiologique, à divers degrés, a été observée chez 97,0% d'entre eux; 50% ont présenté des signes, d'amélioration marquée ou modérée.

A la fin de ce traitement les crachats sont devenus négatifs bactériologiquement dans 77,3% des 66 cas observés. D'après les standards de la "National Tuberculosis Association la "conversion" des crachats s'est produite dans 59,4% des cas au cours d'une période de soixante jours d'observation.

Après la fin du traitement, des cultures positives pour le *M. tuberculosis* ont été obtenues chez 25 des malades ayant reçu la série complète du traitement. Dans chaque cas, ces cultures se sont montrées sensibles à la streptomycine et à la terramycine.

Acknowledgment

The authors wish to express their appreciation to Mr. E. D. Jenkins, biostatistician, for his help in the preparation of the tabular data, and to Miss Ann Wright for her technical assistance.

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COMBINED CORTICOTROPIN (ACTH), PARA-AMINOSALICYLIC ACID (PAS), AND STREPTOMYCIN IN THE TREATMENT OF PULMONARY TUBERCULOSIS[1]

ANDREW H. MEYER, LAURANCE W. KINSELL, AND ROBERT J. PARSONS

(Received for publication March 7, 1952)

During the past year, 1950 to 1951, the writers have treated 3 patients who had far advanced active pulmonary tuberculosis and extensive tracheobronchial tuberculosis with combined corticotropin (ACTH), para-aminosalicylic acid (PAS), and streptomycin.

One of these patients (GB) had a destroyed upper lobe on the right, a fresh tuberculous infiltrate in the right lower lobe, and contralateral stable disease. One (DH) had a giant cavity in the superior segment of the right lower lobe and contralateral stable disease; and one (AS) had a giant cavity in the right upper lobe, a new infiltrate in the right lower lobe, and contralateral unstable disease.

Each of these patients had received maximum benefit from pneumothorax or pneumoperitoneum and had shown no benefit from previous courses of streptomycin and PAS. In the first 2 patients, it was believed that, if the tracheobronchial tree could be made suitable for excision therapy, this procedure should be done.

METHOD

After it had been determined that tubercle bacilli from each patient was susceptible to all concentrations of streptomycin tested, this drug was given for two weeks (1 gm. daily), and 1 gm. twice weekly thereafter. Para-aminosalicylic acid was also administered in a dosage of 5 gm. three times a day. After one week of this regimen, corticotropin in doses which ranged from 12.5 mg. every six hours intramuscularly to 50 mg. intravenously every twelve hours was given.

Absolute eosinophile counts, blood sugar determinations, erythrocyte sedimentation rates, determinations of intracutaneous tuberculin sensitivity (using Old Tuberculin), chest roentgenograms, and bronchoscopic evaluations were done at regular intervals. The patient's weight, blood pressure, and general clinical status were checked daily.

OBSERVATIONS

Laboratory results: The eosinophile response was adequate, dropping from 200 per cu.mm. to 25 or less at the end of eight hours. Blood sugar concentrations were determined weekly and did not become elevated. Erythrocyte sedimentation rates were all elevated at the beginning of therapy and remained so.

Roentgenographic results: One patient (GB) developed atelectasis of the re-

[1] From Arroyo Del Valle, Livermore, California; the Institute for Metabolic Research of Highland Hospital, and the Department of Pathology, Highland Hospital, Oakland, California.

mainder of the right lung and marked enlargement of the cavity in the right upper lobe. No change was noted in the stable left lung (figure 1).

One patient (DH) showed no definite roentgenographic change.

One patient (AS) showed further spread of the infiltrate in the right lung base after five months of combined therapy. There was no improvement in the right upper lobe cavity, but there was some clearing at the base of the unstable lesion in the left lung.

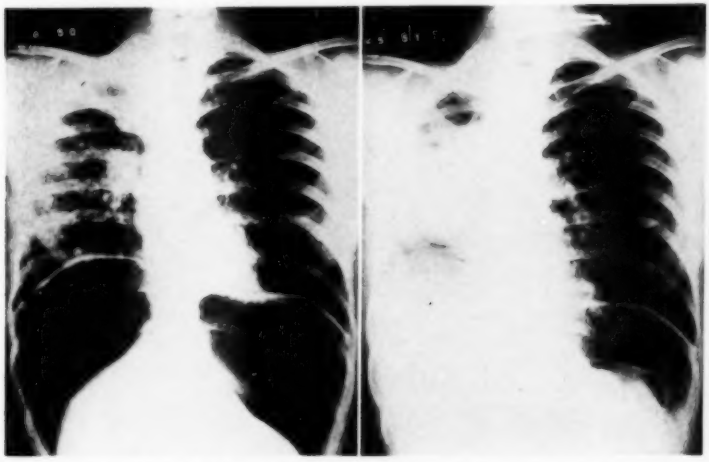

FIG. 1. *Case GB.* (Left) Chest roentgenogram taken prior to combined corticotropin-streptomycin-PAS therapy, showing atelectasis of the right upper lobe with cavitation. There is fibrosis and infiltration throughout the remainder of the right lung. The left lung is clear.

(Right) Chest roentgenogram taken near the termination of the combined corticotropin-streptomycin-PAS therapy, showing enlargement of the cavity in the right upper lobe and atelectasis of the remainder of the right lung.

In no instance was improvement noted in the roentgenographic examinations of the lungs which were done at weekly intervals (figure 2).

Bronchoscopic results:[2] Prior to combined therapy, January 29, 1951, patient GB had extensive ulceration of the tracheal mucosa from the midportion extending down the right main stem bronchus. The right main stem bronchus just admitted a No. 4 bronchoscope. Within three weeks, the tracheal mucosa appeared normal, as did the mucosa of the right main stem bronchus except for a small area of redness and ulceration around the right upper lobe opening. The stenotic area in the right main stem bronchus persisted. A right pneumonectomy was done on June 19, 1951.

Patient DH had shown redness, edema, and marked friability of the entire

[2] All bronchoscopies were performed by Dr. J. Hallam Cope, Oakland, California.

trachea and the right main bronchus. No ulcerations or granulation tissue were noted, but the appearance of the tracheobronchial mucosa made operation inadvisable in the opinion of the surgical consultants. Within seventy-two hours after corticotropin was begun, December 16, 1951, the mucosa showed only

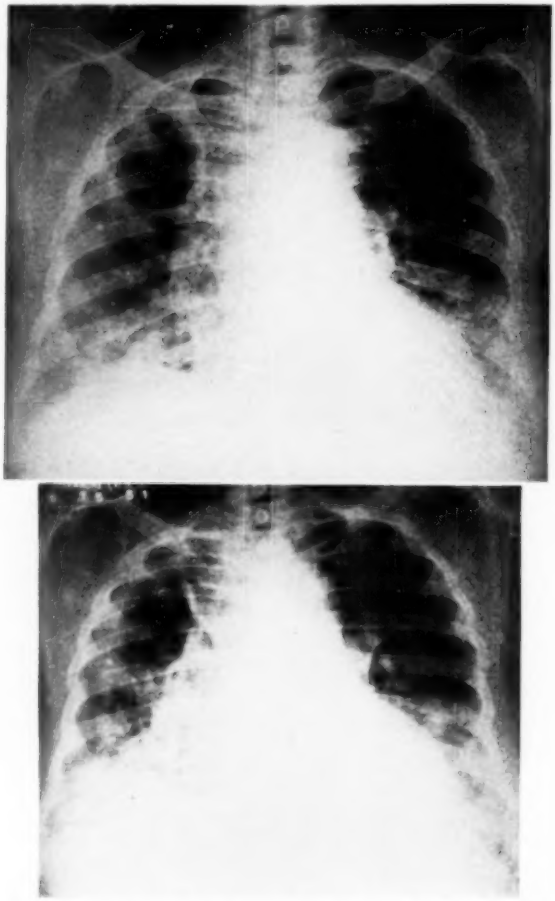

FIG. 2. *Case A.S.* (Top) Chest roentgenogram taken shortly after beginning of combined corticotropin-streptomycin-PAS therapy, showing a cavity in the right upper lobe with infiltration in both lung bases.

(Bottom) Chest roentgenogram taken at the termination of combined corticotropin-streptomycin-PAS therapy, showing no improvement in the right upper cavity and increase of density in the right base. There has been clearing in the left base.

thickening and the lesion was deemed to be operable. However, this improvement in the bronchoscopic picture was maintained for a period of six weeks only and then, despite continued combined therapy, the tracheobronchial mucosa again became red and very friable. Corticotropin was discontinued on May 8, 1951, and streptomycin and PAS were continued. By May 21, 1951, the mucosa had again become free of redness and friability. Excision therapy was undertaken on May 25, 1951.

In the third patient (AS), no improvement was noted in the bronchoscopic picture at the end of five months of combined therapy.

Clinical results: Each of the 3 patients developed a marked sense of well-being within the first week of corticotropin therapy. All had marked decrease in cough, and 2 patients who had been troubled by wheezing became free of this complaint within seventy-two hours of beginning the drug. All showed a drop in their temperatures to nearly normal levels.

The intracutaneous test with OT, which had measured up to 1 cm. induration with 0.01 mg., was only 0.25 cm. with 1.0 mg. of OT at the end of seventy-two hours of corticotropin therapy. In one instance, 10 mg. of OT given intracutaneously produced only 1 cm. induration at the end of forty-two and seventy-two hours. No systemic reaction resulted from this massive dose of Old Tuberculin.

Operative results: The first patient (GB), who had a right pneumonectomy, developed a bronchopleural fistula on the tenth postoperative day and died on the twelfth postoperative day. Patient DH, who had a right lower lobe removed and the remaining lobes decorticated, developed acute left ventricular failure on the second postoperative day and died on the third day. This patient was twenty-seven years old.

Microscopic report: In each instance there was extensive destruction of the bronchial cartilages, and active caseous tuberculous bronchitis was present. In the lung there were areas of ordinary fibrocaseous tuberculosis as well as many areas of caseation which showed no evidence of surrounding fibrosis and little, and in some areas no, epithelioid granulation tissue around them. In the opinion of the pathologist, Dr. Robert J. Parsons, the latter areas had the appearance of an acute fulminating tuberculous infection without the usual attempts at healing. They resembled the lesions seen in the caseous pneumonia which develops as the result of aspiration of caseous material in the lung of a sensitized individual.

Examination of the bronchial stump in the patient in whom the bronchopleural fistula had developed showed that the incision had been through an area of tuberculous bronchitis. Although the patient died on the twelfth postoperative day, the edges of the stump showed little granulation tissue.

A complete post-mortem examination of patient GB did not show evidence of miliary spread of tuberculosis. The adrenal glands of this patient were interpreted as showing lipoid exhaustion with moderate hypertrophy of the cortex.

SUMMARY

Three patients with extensive tracheobronchial tuberculosis complicating essentially unilateral pulmonary tuberculosis, which had failed to respond to

adequate trials of pneumoperitoneum, pneumothorax, para-aminosalicylic acid (PAS), and streptomycin, were treated with a regimen of corticotropin (ACTH). streptomycin, and PAS.

Two of the patients showed such striking apparent improvement in the bronchoscopic appearance of the tracheobronchial tree that excision therapy was thought to be possible. Both of these patients died postoperatively; one from the development of a bronchopleural fistula, the other from acute left ventricular failure.

Microscopic examination of the surgically excised specimens showed areas of typical caseation necrosis with good fibrous tissue response, but also areas of caseation necrosis with no surrounding fibrous tissue. Examination of the bronchial stump of the patient who developed the bronchopleural fistula showed little attempt at healing in the severed end, as well as extensive bronchial tuberculosis.

Further very cautious studies are needed to determine the efficacy of a corticotropin-streptomycin-PAS regimen in preparing a tracheobronchial tree for excision therapy only after other methods have failed.

In the light of the present dosage of corticotropin, the doses of this drug which were used intravenously were excessive.

SUMARIO

La Combinación de Corticotropina (HACT), Acido Para-Aminosalicílico (PAS) y Estreptomicina en el Tratamiento de la Tuberculosis Pulmonar

Tres enfermos con tuberculosis traqueobronquial difusa que complicaba una tuberculosis pulmonar esencialmente unilateral y que no había respondido a ensayos adecuados del neumoperitoneo, del neumotórax, del ácido para-aminosalicílico (PAS) y de la estreptomicina, feuron tratados con un régimen de corticotropina (HACT), estreptomicina y PAS.

Dos de los enfermos mostraron tan notable mejoría aparente en el aspecto broncoscópico del árbol traqueobronquial que se creyó posible aplicar la excisión terapéutica. Ambos sujetos fallecieron postoperatoriamente: uno de la formación de una fístula broncopleural y el otro de insuficiencia aguda del ventrículo izquierdo.

El examen microscópico de los ejemplares excindidos reveló zonas de típica necrosis-caseación con buena reacción de tejido fibroso, pero también otras de necrosis-caseación sin tejido fibroso circundante. El examen del muñón bronquial del enfermo que manifestó fístula broncopleural mostró pocos conatos de cicatrización en el extremo resecado y además tuberculosis bronquial difusa.

Necesítanse más estudios cautelosísimos para determinar la eficacia de un régimen de corticotropina-estreptomicina-PAS en la preparación de un árbol traqueobronquial para la intervención cruenta después de fracasar otros métodos.

A la luz de la posología actual de la corticotropina, fueron excesivas las dosis endovenosas de la droga que se usaron.

RESUME

Association corticotrophine (ACTH), acide para-aminosalicylique (PAS), et streptomycine dans le traitement de la tuberculose pulmonaire

Trois malades atteints de tuberculose trachéo-bronchique extensive compliquant une tuberculose pulmonaire essentiellement unilatérale, et qui n'avait pas répondu à des tentatives adéquates de traitement par pneumopéritoine, pneumothorax, acide para-aminosalicylique (PAS) et streptomycine, ont été traités par l'association corticotrophine (ACTH) streptomycine et PAS.

Deux de ces malades ont fourni la preuve bronchoscopique d'une amélioration si saisissante de l'aspect de l'arbre tréchéo-bronchique qu'une thérapeutique d'excision á paru possible. Ces deux malades sont morts aprés l'intervention, l'un d'une fistule broncho-pleurale, l'autre d'une défaillance aiguë du ventricule gauche.

L'examen histologique des tissus excisés a montré des zones caractéristiques de nécrose avec caséification et une bonne formation de tissu fibreux périphérique. L'examen du moignon bronchique du sujet ayant présenté la fistule broncho-pleurale ne révélait que peu de tendance à la cicatrisation dans le bout sectionné ainsi q'une tuberculose bronchique extensive.

De plus amples études trés prudentes sont nécessaires pour déterminer l'efficacité d'un traitement combiné corticotrophine-streptomycine-PAS pour préparer l'arbre trachéo-bronchique à la thérapeutique d'excision, quand les autres procédés ont échoué.

A la lumière de la posologie actuelle de la corticotrophine, les doses intraveineuses de cette substance qui ont été utilisées sont jugées excessives.

A STUDY OF THE POSITIVE ROENTGENOGRAPHIC FINDINGS FOR THE 1948 WASHINGTON MASS SURVEY[1]

Two-Year Status

HOWARD M. PAYNE, PHILIP ENTERLINE, AND JULIA HEUCK

(Received for publication March 26, 1952)

INTRODUCTION

In 1948, the Tuberculosis Division of the Public Health Service, the District Health Department, the District of Columbia Tuberculosis Association, and the medical societies organized in the District of Columbia one of the first fast-tempo chest roentgenographic surveys of a large city area. Civic leaders and groups in all walks of life participated in the organization of this survey. To almost all concerned it was a relatively new venture. The magnitude of the effort, its successes, and failures must be regarded in this light.

The broad objectives which the survey hoped to accomplish can be stated. The specific benefits expected from the survey were too numerous to be catalogued in detail.

Objectives of the Survey

1. To find the previously unknown patients with tuberculosis in the District of Columbia.
2. To place these tuberculous patients under adequate medical care.
3. To learn the prevalence of tuberculosis in the city and in the various parts of the population by age, sex, race, and area.
4. To find by study of the survey results what services and facilities are fundamentally necessary for the improved prevention and control of tuberculosis in the District of Columbia.
5. To develop new programs of community organization, public organization, and research, based upon the findings of the survey.
6. To observe the patients found by the survey for a period of two years in order to discover a sound technical basis for the medical, nursing, public health, and rehabilitation procedures necessary for tuberculosis prevention and control in the District of Columbia.

Under the leadership of Dr. Arthur C. Christie, a medical technical committee undertook the planning and guidance of the medical, nursing, social work, and public health aspects of the survey. The present follow-up study is the result of

[1] This report is made on behalf of the Medical Technical Committee, Washington Chest X-ray Survey:

Dr. W. Leroy Dunn — Mr. Edward K. Funkhouser
Mr. Philip Enterline — Miss Julia Heuck
Dr. Daniel L. Finucane — Dr. Vernon M. Padgett
Dr. John Trenis
Dr. Arthur C. Christie, *Chairman*
Dr. Howard M. Payne, *Vice Chairman*

the planning carried on by a small segment of that committee reconvened in 1950 for that purpose.

OBSERVATIONS

The Survey Process

Response: Between January 12, and June 30, 1948, 503,414 chest roentgenograms were taken in the District of Columbia. Of this number, 454,130 were taken by the survey organization. It is upon these films that subsequent observations are based. When the unsatisfactory films are eliminated, there remain 440,339 persons actually examined by the survey organization. Unsatisfactory

TABLE 1

WASHINGTON, D. C., CHEST ROENTGENOGRAPHIC SURVEY

NUMBER AND PER CENT OF RESIDENT POPULATION EXAMINED BY RACE AND AGE

AGE GROUP	TOTAL			WHITE			NON-WHITE		
	Total	Number	Per cent	Total	Number	Per cent	Total	Number	Per cent
Total	861,000*	352,600†	41	616,476	241,048	39	244,524	109,509	45
Under 15	160,765	1,027	1	105,812	571	1	54,953	445	1
Total 15+‡	700,235	351,573	50	510,664	240,477	47	189,571	109,064	58
15 to 24	154,621	84,186	54	112,026	53,349	48	42,595	30,375	71
25 to 34	186,113	102,445	55	131,507	66,745	51	54,606	35,232	65
35 to 44	141,996	73,864	52	99,894	49,717	50	42,102	23,776	56
45 to 54	103,879	51,369	49	77,726	38,821	50	26,153	12,247	47
55 to 64	64,182	26,977	42	49,762	21,858	44	14,420	4,972	34
65 to 74	36,063	9,113	25	28,851	7,464	26	7,212	1,607	22
75+	13,381	2,034	15	10,898	1,679	15	2,483	342	14
Unknown		1,585			844			513	

* Bureau of the Census estimate as of July 1, 1947.

† The age and race distribution of examinations are based on a 29 per cent sample of the Survey records. Includes race unknown.

‡ Including age unknown.

films are excluded from the following discussion since, for the most part, the persons concerned returned for another film and are already counted in the satisfactory film totals.

Of the total persons examined, 352,600 (80 per cent) were residents of the District of Columbia. As shown in table 1, this number represents 41 per cent of the estimated population: 39 per cent of the white population and 45 per cent of the non-white population. In terms of the population considered eligible for roentgenographic examination, however, persons fifteen years of age and over, the response for examination by the survey was 50 per cent. Approximately 47 per cent of the eligible white population and 58 per cent of the non-white responded for examination.

As may be seen in table 1 and in figure 1, response in the age group "55 and

over" dropped off considerably for both the whites and non-whites. The response in the "15 to 54" age group was 53 per cent, compared with 34 per cent in the group "55 and over" (not grouped in table 1).

Film findings: Of the total 440,339 satisfactory examinations, 70 mm. small film positives amounted to 21,858 (5 per cent), of which 12,464 (2.8 per cent) were called positive for suspected tuberculosis; 4,532 (1 per cent), positive for cardiac abnormalities; and 4,862 (1.1 per cent), positive for other abnormalities of the lung. All but 823 of the persons with positive films were recalled for a 14- by 17-inch film. The 823 not recalled were persons with suspected cardiac disease and reflected a policy in effect during part of the survey of referring this group directly for diagnosis without a 14- by 17-inch film.

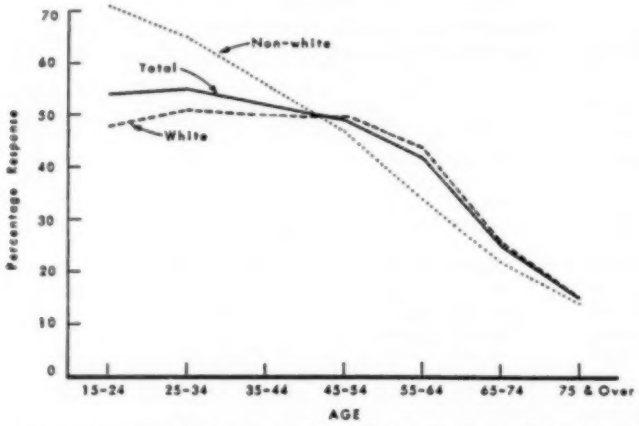

FIG. 1. Percentage response by age and race of the eligible population (age 15 years and over).

Of the 21,035 persons recalled, 18,191 (86.5 per cent) returned for a 14- by 17-inch chest film. An additional 708 (3.4 per cent) preferred to go directly to a private physician or clinic, while 184 (approximately 1 per cent) lived outside the metropolitan area or were unable to come for other reasons. Of the remaining 1,952 persons, 1,535 were finally considered not significant for follow-up for either technical or administrative reasons, and 417 persons (2 per cent of those recalled) were finally considered lost or uncooperative.

In table 2 the results of 14- by 17-inch film examinations at the Weightman School X-ray center are shown. The 6,519 persons who showed evidence or suspected evidence of tuberculosis on 14- by 17- inch film were referred to a health department chest clinic for study. Persons who had suspected thoracic illnesses other than tuberculosis were referred to their private physicians, and complete records of their subsequent diagnoses are not available. As of December 31, 1948, or six months after the close of the survey, of the 6,519 tuberculosis suspects referred for diagnosis, only 139 (2 per cent) had not responded.

In table 3 are described the initial clinical findings in relation to the original 14- by 17-inch film readings at Weightman School on the 6,380 persons who

TABLE 2

WASHINGTON, D. C., CHEST ROENTGENOGRAPHIC SURVEY

14- BY 17-INCH FILM READINGS AT THE WEIGHTMAN SCHOOL X-RAY CENTER

14-BY 17-INCH FILM READINGS	NUMBER	PER CENT OF 14- BY 17-INCH FILMS TAKEN	PER CENT OF PERSONS EXAMINED
Total persons examined	440,339		100.0
Total 14- by 17-inch films taken	18,603*	100.0	
Negative	7,734	41.6	
Tuberculosis and suspected tuberculosis	6,519	35.0	1.5
Reinfection type of tuberculosis	4,476	24.1	1.0
Minimal (84%)	3,756		
Moderately advanced (13%)	578		
Far advanced (3%)	142		
Other tuberculosis	309	1.7	0.1
Suspected tuberculosis	1,734	9.3	0.4
Cardiac disease	2,072	11.1	0.5
Other pathology	2,278	12.2	0.5

* Includes 412 persons who did not have a satisfactory 70 mm. film. These 412 persons are included in total persons examined.

TABLE 3

WASHINGTON, D. C., CHEST ROENTGENOGRAPHIC SURVEY

COMPARISON OF FINDINGS ON 14- BY 17-INCH FILMS WITH FINDINGS BASED UPON FOLLOW-UP ROENTGENOGRAPHIC AND CLINICAL EVIDENCE

FINDINGS ON 14- BY 17-INCH FILM	TOTAL		FINDINGS ON FOLLOW-UP ROENTGENOGRAPHIC AND CLINICAL EVIDENCE									
			Minimal		Moderately Advanced		Far Advanced		Tuberculosis Status not Given		Negative for Tuberculosis	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Total	6,380	100.0	2,536	39.7	920	14.4	256	4.0	663	10.4	2,005	31.4
Minimal	3,687	100.0	1,888	51.2	469	12.7	48	1.3	411	11.1	871	23.6
Moderately advanced	554	100.0	111	20.0	271	48.9	62	11.2	37	6.7	73	13.2
Far advanced	137	100.0	2	1.5	21	15.3	68	49.6	14	10.2	32	23.4
Other tuberculosis	251	100.0	34	13.5	71	28.3	68	27.1	22	8.8	56	22.3
Suspected tuberculosis type and/or stage not given	1,751	100.0	501	28.6	88	5.0	10	0.6	179	10.2	973	55.6

reported for clinical evaluation of the roentgenographic findings by the end of 1948.

The Prevalence of Pulmonary Tuberculosis in the District of Columbia

In planning a control program for tuberculosis, it is important to estimate the prevalence of unknown tuberculosis in a community. Shown in table 4 are residents of the District examined, new cases of tuberculosis discovered, and rates

TABLE 4

WASHINGTON, D. C., CHEST ROENTGENOGRAPHIC SURVEY

PREVALENCE OF NEW TUBERCULOSIS AMONG RESIDENTS EXAMINED BY AGE AND RACE

AGE AND RACE	NUMBER OF RESIDENTS EXAMINED	NEW CASES FOUND	RATE PER 1,000 RESIDENTS EXAMINED
Total 15 years and over	349,988*	2,758	7.9
15 to 54 years	311,864	1,604	5.1
55 and over	38,124	1,154	30.3
White population, 15 years and over	239,633	2,063	8.6
15 to 54 years	208,632	1,114	5.3
55 and over	31,001	949	30.6
Non-white population, 15 years and over	108,551	684	6.3
15 to 54 years	101,630	482	4.7
55 and over	6,921	202	29.2

* Includes race unknown. Excludes age unknown.

TABLE 5

WASHINGTON, D. C., CHEST ROENTGENOGRAPHIC SURVEY FOLLOW-UP STUDY

ESTIMATED NUMBER OF TUBERCULOSIS CASES KNOWN AND UNKNOWN IN WASHINGTON, D. C.

AGE GROUPS	TOTAL POPULATION	POPULATION EXAMINED	DISCOVERY RATE IN POPULATION EXAMINED PER 1,000	UNEXAMINED POPULATION (1) − (2)	PREDICTED UNKNOWN CASES IN UNEXAMINED POPULATION (3) × (4)	TOTAL KNOWN CASES*	KNOWN CASES PER 1,000 POPULATION (6)/(1) × 1,000	TOTAL ESTIMATED CASES IN DISTRICT OF COLUMBIA (5) + (6)	ESTIMATED TOTAL CASES PER 1,000 POPULATION (8)/(1) × 1,000
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Total, 15 years and over	700,235†	349,988	—	350,247	3,689	6,829	—	10,518	—
15 to 54 years	586,609	311,864	5.1	274,745	1,401	5,369	9.1	6,770	11.5
55 years and over	113,626	38,124	30.3	75,502	2,288	1,460	12.8	3,748	33.0

* Registered at end of 1948 including Survey cases.

† Bureau of the Census estimate as of July 1, 1947.

per 1,000 residents examined by age and race. Residents are defined as persons giving home addresses in the District of Columbia. New cases are defined as resident cases of tuberculosis unknown to the health department tuberculosis case register prior to the survey. Study of these data reveals a high prevalence

of tuberculosis among the older age groups. Over 40 per cent of the tuberculosis patients were found among persons aged 55 and over despite the fact that this older group comprised approximately only 10 per cent of those examined. This disproportion in prevalence holds for both whites and non-whites. The differences in rates are highly significant statistically.

In table 5 a projection of the prevalence rates shown in table 4 into the unexamined population and an estimate of the total cases present in the District of Columbia at the time of the survey are shown. Here it is predicted that there were 10,500 District residents with tuberculosis in 1948, of whom 65 per cent were known at the end of the survey. Among the residents in the 15 to 54 age group, 79 per cent of the total cases were known; but *among those 55 years of age and over, only 39 per cent were known* (figure 2).

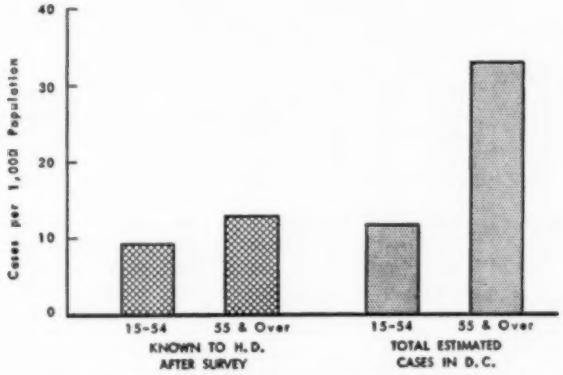

FIG. 2. Prevalence of known and total tuberculosis after the District of Columbia survey, by age.

The Follow-up of Diagnosed Cases Found by Survey

Of the 4,375 diagnosed cases of tuberculosis processed by the survey (shown in table 3), 3,373 occurred in District of Columbia residents, of whom 2,776 were previously unknown to the District of Columbia Health Department (2,758 of these were more than 15 years of age and are shown in table 4). It was the purpose of the survey follow-up study to discover pertinent facts about the subsequent status of these new patients. It was planned to follow all of the 2,776 "resident cases" of tuberculosis discovered by the survey, *regardless of subsequent diagnoses*, by periodic examinations at a clinic or by the person's private physician for a period of at least two years. All such survey cases were kept in a separate file of the tuberculosis register in order to implement special administrative procedures applying only to this group. At the end of the two-year period all records were coded and tabulated for initial, interim, and last diagnoses. Reported here are some of the findings of this follow-up study.

Deaths during follow-up period: Of the 2,776 "resident cases" discovered by the survey, 438 (16 per cent) moved away or died before the end of the twenty-four-month follow-up period. There were, therefore, on the average, 2,557[2] persons who could be observed for death during this two-year period.

TABLE 6

WASHINGTON, D. C., CHEST ROENTGENOGRAPHIC SURVEY FOLLOW-UP STUDY (1)

PROBABILITY OF TUBERCULOSIS DEATH DURING THIRTY-MONTH OBSERVATION PERIOD BY ORIGINAL CLINICAL STATUS

New Cases—District of Columbia Residents Only

ORIGINAL CLINICAL STATUS AND TIME INTERVAL	NUMBER PRESENT AT BEGINNING OF PERIOD l_x	NUMBER WITHDRAWN DURING PERIOD w_x	NUMBER DYING (TUBERCULOSIS) DURING PERIOD d_x	AVERAGE NUMBER AT RISK $l_x - 1/2w_x$	PERCENTAGE DYING IN GIVEN PERIOD $100\ q_x$	PERCENTAGE SURVIVING IN GIVEN PERIOD $100\ p_x$	PERCENTAGE SURVIVING THROUGH PRECEDING AND CURRENT PERIOD $100\ hp_x$	PERCENTAGE DYING IN PRECEDING AND CURRENT PERIOD $100\ hq_x$
months								
Total								
Less than 6	2,776	249	11	2,651.5	0.41	99.59	99.59	0.41
6 to 12	2,516	78	17	2,477.0	0.69	99.31	98.90	1.10
12 to 18	2,421	61	13	2,390.5	0.54	99.46	98.37	1.63
18 to 24	2,347	50	10	2,322.0	0.43	99.57	97.95	2.05
24 to 30	2,287	37	10	2,268.5	0.44	99.56	97.52	2.48
Active*								
Less than 6	654	71	8	618.5	1.29	98.71	98.71	1.29
6 to 12	575	29	9	560.5	1.61	98.39	97.12	2.88
12 to 18	537	24	7	525.0	1.33	98.67	95.83	4.17
18 to 24	506	12	4	500.0	0.80	99.20	95.06	4.94
24 to 30	490	9	4	485.5	0.82	99.18	94.28	5.72
Inactive†								
Less than 6	1,588	128	—	1,524.0	0.00	100.00	100.00	0.00
6 to 12	1,460	27	1	1,446.5	0.07	99.93	99.93	0.07
12 to 18	1,432	25	2	1,419.5	0.14	99.86	99.79	0.21
18 to 24	1,405	27	1	1,391.5	0.07	99.93	99.72	0.28
24 to 30	1,377	23	2	1,365.5	0.15	99.85	99.57	0.43
Activity not stated								
Less than 6	534	50	3	509.0	0.59	99.41	99.41	0.59
6 to 12	481	22	7	470.0	1.49	98.51	97.93	2.07
12 to 18	452	12	4	446.0	0.90	99.10	97.05	2.95
18 to 24	436	11	5	430.5	1.16	98.84	95.92	4.08
24 to 30	420	5	4	417.5	0.96	99.04	95.00	5.00

* Includes active, quiescent, and questionably active.

† Includes inactive, apparently arrested, arrested, and apparently cured.

A total of 100 persons died (from all causes) during the follow-up period. This is an average annual death rate of 1,955 per 100,000, or approximately twice as

[2] Computed as follows: $2,776 - \frac{1}{2}(438)$. This assumes that those persons who had moved or died were, on the average, exposed to risk for one year and, therefore, one-half the weight of this group should be added to the number present for the full period in order to estimate death rates.

high as the expected crude mortality (1,007 per 100,000 in 1949) for the District of Columbia. If tuberculosis deaths are excluded, of which there were 51, or approximately one-half of the total, the annual average death rate was 1,017, or only slightly higher than the crude death rate, excluding tuberculosis, for the District of Columbia in 1949 of 955 per 100,000. Some or all of the difference may be explained by the fact that the cases of tuberculosis followed occurred in somewhat older persons than the average District of Columbia resident. It cannot be established with certainty that all the nontuberculous deaths were "cleared" routinely with the registry as were those for tuberculosis.

The average annual death rate for tuberculosis in the study group was 997 per 100,000, or nearly twenty times as great as the District tuberculosis death rate of 52 recorded in 1949.

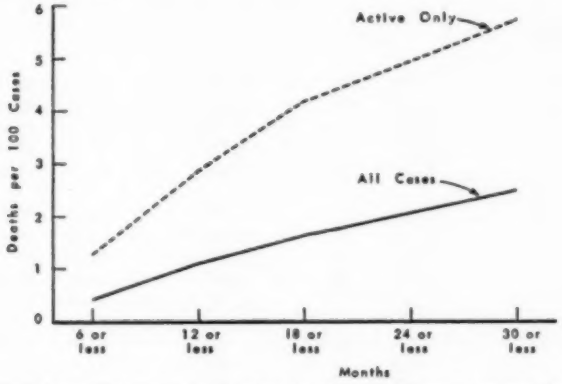

FIG. 3. Deaths per 100 new cases, showing initially active cases separately, cumulated in successive six-month intervals.

Data are available regarding deaths from tuberculosis for a full thirty months after the original diagnosis, since the survey register was maintained for that period and records were not actually coded until after thirty months had elapsed. During this thirty-month period there was a total of 61 deaths from tuberculosis. The probabilities of death by original activity and by six-month intervals are shown in table 6 and figure 3. Here it may be seen that the probability of dying of tuberculosis within the thirty-month period was 2.48 per cent. This varied from 5.72 per cent for those cases originally considered "active" to 0.43 per cent for those considered inactive. It is interesting that the "activity not stated" group showed a probability of dying which was nearly as high as for the active group.

In table 7 and figure 4, the probabilities of dying from tuberculosis by the stage of disease on original diagnosis are shown. As might be expected, these ranged from a high of 23.73 per cent for the far advanced group to 0.51 per cent for the minimal and clearly demonstrate the poor prognosis for the former group.

The patients who were given no definite diagnosis of the stage of disease or who were diagnosed "positive pathology," "suspected," or given other diagnostic appellations indicative of uncertainty on the part of the clinicians, showed a

TABLE 7

WASHINGTON, D. C., CHEST ROENTGENOGRAPHIC SURVEY FOLLOW-UP STUDY (1)
PROBABILITY OF TUBERCULOSIS DEATH DURING THIRTY-MONTH OBSERVATION PERIOD BY ORIGINAL DIAGNOSIS
New Cases—District of Columbia Residents Only

TIME INTERVAL	NUMBER PRESENT AT BEGINNING OF PERIOD l_x	NUMBER WITHDRAWN DURING PERIOD w_x	NUMBER DYING (TUBERCULOSIS) DURING PERIOD d_x	AVERAGE NUMBER AT RISK $l_x - 1/2w_x$	PERCENTAGE DYING IN GIVEN PERIOD 100 q_x	PERCENTAGE SURVIVING IN GIVEN PERIOD 100 p_x	PERCENTAGE SURVIVING THROUGH PRECEDING AND CURRENT PERIOD 100 hp_x	PERCENTAGE DYING IN PRECEDING AND CURRENT PERIOD 100 hq_x
months								
Total								
Less than 6	2,776	249	11	2,651.5	0.41	99.59	99.59	0.41
6 to 12	2,516	78	17	2,477.0	0.69	99.31	98.90	1.10
12 to 18	2,421	61	13	2,390.5	0.54	99.46	98.37	1.63
18 to 24	2,347	50	10	2,322.0	0.43	99.57	97.95	2.05
24 to 30	2,287	37	10	2,268.5	0.44	99.56	97.52	2.48
Minimal								
Less than 6	1,530	110	1	1,475.0	0.07	99.93	99.93	0.07
6 to 12	1,419	35	2	1,401.5	0.14	99.86	99.79	0.21
12 to 18	1,382	30	1	1,367.0	0.07	99.93	99.72	0.28
18 to 24	1,351	28	2	1,337.0	0.15	99.85	99.57	0.43
24 to 30	1,321	19	1	1,311.5	0.08	99.92	99.49	0.51
Moderately advanced								
Less than 6	439	46	1	416.0	0.24	99.76	99.76	0.24
6 to 12	392	13	2	385.5	0.52	99.48	99.24	0.76
12 to 18	377	10	4	372.0	1.08	98.92	98.17	1.83
18 to 24	363	8	1	359.0	0.28	99.72	97.90	2.10
24 to 30	354	9	2	349.5	0.57	99.43	97.34	2.66
Far advanced								
Less than 6	103	11	7	97.5	7.18	92.82	92.82	7.18
6 to 12	85	4	6	83.0	7.23	92.77	86.11	13.89
12 to 18	75	4	4	73.0	5.48	94.52	81.39	18.61
18 to 24	67	4	2	65.0	3.08	96.92	78.88	21.12
24 to 30	61	1	2	60.5	3.31	96.69	76.27	23.73
Suspected possible pathology and all other								
Less than 6	704	82	2	663.0	0.30	99.70	99.70	0.30
6 to 12	620	26	7	607.0	1.15	98.85	98.55	1.45
12 to 18	587	17	4	578.5	0.69	99.31	97.87	2.13
18 to 24	566	10	5	561.0	0.89	99.11	97.00	3.00
24 to 30	551	8	5	547.0	0.91	99.09	96.12	3.88

probability of dying that was somewhat greater than that for patients diagnosed "moderately advanced." The lack of bacteriologic aids to diagnosis may have been a major reason for diagnostic uncertainty here. Another factor may have

been an insufficient number of clinic visits to establish a definite early diagnosis. Shortages of medical and nursing personnel could account for this factor.

Unfavorable changes in activity and stage of disease during period: It was originally planned to follow all the new "resident cases" by periodic examinations. Not all of these persons responded for examination as requested, however, so that a loss considerably greater than that tabulated for mortality observation occurred. Whereas the only persons leaving observation for mortality were those who died or moved, persons leaving observation for changes in activity or stage of disease consisted of all those who, for any reason, did not have a satisfactory observation at the twenty-four-month period. Of the total 2,776 residents

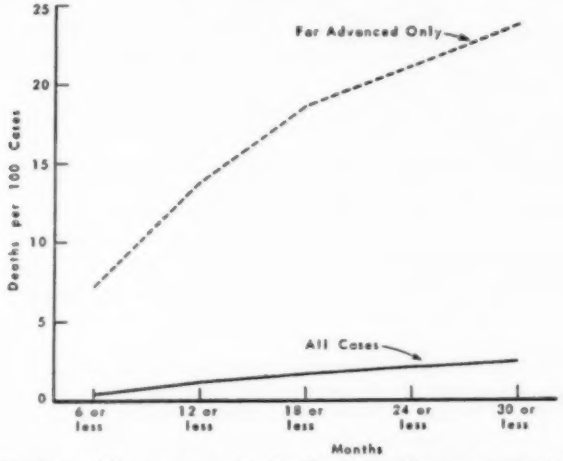

FIG. 4. Deaths per 100 new cases, showing far advanced cases separately, cumulated in successive six-month intervals.

initially diagnosed, only 1,823 (68.7 per cent) were observed at the twenty-four-month period.

The remaining 953 persons were last observed at varying lengths of time after the original diagnosis. If it be assumed that, on the average, these patients were observed for approximately one year, it is possible to compute the average number at risk of an unfavorable diagnosis or activity classification during the twenty-four-month observation period. Probabilities of an unfavorable activity classification for "inactive," and "activity unknown" cases are shown in table 8. The probability of subsequent unfavorable status of almost 10 per cent for patients thought to have inactive lesions on early evaluation is contrasted with a probability of 42 per cent when the activity of the lesion is unknown or unstated. This is attributable to the fact that progression of the disease on serial roentgenographic examination was a major criterion of activity in many instances in which laboratory and other medical facilities were lacking.

The probabilities that the 1,969 minimal and moderately advanced cases diagnosed early will progress to a more advanced stage in twenty-four months are shown in table 9. The probability of progression for a minimal case is shown

TABLE 8

WASHINGTON, D. C., CHEST ROENTGENOGRAPHIC SURVEY FOLLOW-UP STUDY (1)

PROBABILITY OF UNFAVORABLE ACTIVITY STATUS FOR CASES INITIALLY INACTIVE AND ACTIVITY UNKNOWN DURING A TWENTY-FOUR-MONTH OBSERVATION PERIOD

New Cases—District of Columbia Residents Only

ORIGINAL ACTIVITY	NUMBER PRESENT AT BEGINNING	NUMBER WITHDRAWN BEFORE 24 MONTHS	AVERAGE NUMBER AT RISK (1) − 1/2 (2)	ACTIVE* AT SOME TIME BUT NOT TUBERCULOSIS DEATH		PROBABILITY OF TUBERCULOSIS DEATH†	PROBABILITY OF TUBERCULOSIS DEATH OR ACTIVE AT SOME TIME (5) + (6)
				Number	Probability (4) ÷ (3) × 100		
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Total inactive and activity unknown	2,122	713	1,765.5	292	16.54	1.22	17.76
Inactive‡	1,588	510	1,333.0	127	9.52	0.28	9.80
Activity unknown	534	203	432.5	165	38.15	4.08	42.23

* Includes active, quiescent, and questionably active.

† At 24 months from table 6.

‡ Includes inactive, apparently arrested, arrested, and apparently cured.

TABLE 9

WASHINGTON, D. C., CHEST ROENTGENOGRAPHIC SURVEY FOLLOW-UP STUDY (1)

PROGRESSION TO MORE ADVANCED STAGE FOR CASES INITIALLY MINIMAL AND MODERATELY ADVANCED DURING A TWENTY-FOUR-MONTH OBSERVATION PERIOD

New Cases—District of Columbia Residents Only

ORIGINAL STAGE	NUMBER PRESENT AT BEGINNING	NUMBER WITHDRAWN BEFORE 24 MONTHS	AVERAGE NUMBER AT RISK (1) − ½(2)	PROGRESSED BUT NOT TUBERCULOSIS DEATH		PROBABILITY OF TUBERCULOSIS DEATH*	PROBABILITY OF TUBERCULOSIS DEATH OR MORE ADVANCED STAGE (5) + (6)
				Number	Probability (4) ÷ (3) × 100		
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Total minimal and moderately advanced	1,969	579	1,679.5	155	9.23	0.80	10.03
Minimal	1,530	427	1,316.5	124	9.42	0.43	9.85
Moderately advanced	439	152	363.0	31	8.54	2.10	10.64

* At 24 months from table 7.

here to be approximately the same as that for a moderately advanced case. The death rate for persons with moderately advanced lesions in twenty-four months of observation is five times that for "minimals."

Last Known Supervision

In order to gain an idea of what community facilities carry responsibility for patient follow-up, a group of 3,651 new patients, not corrected for residence, was tabulated by last reported supervision without regard to length of observation or losses. It is interesting that almost two-thirds of the patients with tuberculous lesions reported as active, questionably active, or quiescent were under ambulant care in the clinics, while approximately one-fourth were hospitalized and only 8 per cent were under private medical care.

DISCUSSION

The two year follow-up period was anticipated before the start of the survey, and certain definite agreements were made concerning the categories of patients who would be followed. There was, however, no carefully formulated protocol of procedures which would ensure uniformity of efforts to bring patients back.

The codes and tabulations for this survey were established nearly two years after it began. Ideally, they should have been carefully prepared beforehand. This would have given clinics, physicians, nurses, and others definite criteria for records of case studies. Such a plan would have rendered the task of follow-up easier and more uniform.

Terminology in use by physicians was not uniform at the time of the original clinic visit. The use of diagnostic terms such as "negative tuberculosis follow" and "positive pathology" makes subsequent comparisons difficult. Tabulations indicate that more than 80 per cent of the groups diagnosed "negative tuberculosis follow" and "positive pathology" were later diagnosed "tuberculous." These patients became "lost" at a greater rate than those diagnosed in more conventional terms.

Bacteriologic study of patients adequate for the determination of a contagious status is not evident from the records. Gastric washings for cultures for tubercle bacilli could not be made for clinic patients without referral to private facilities. A review of the data indicates that determinations of activity were made largely upon the basis of roentgenographic change and clinical symptoms.

If follow-up data for patients found in surveys are to serve a useful epidemiological purpose, consideration should be given in the future to the establishment of a record which will show the status on study of all survey patients at regular intervals. This should be based upon life-table procedure (tables 10 and 11).

The prevalence data from the survey are significant. The indication that tuberculosis is approximately six times more prevalent after 54 years of age than between 15 and 54 years is of practical importance.

Certainly, case finding can be directed with increasing intensity toward the older citizen. Our educational campaign should stress the prevalence of morbidity rather than death rates. The former emphasis upon the death rate as a method of estimating the degree of control of tuberculosis has given many groups in this community a false sense of security.

Due to the impact of aging, intercurrent illness, degenerative diseases, accumulated stresses, and physical overstrain upon these older patients, it is of great

importance to know of the presence of both the active and inactive lesions of tuberculosis.

The prevention of progressive and contagious tuberculosis in these patients may depend upon good general medical care, psychosomatic studies and advice, and upon the prevention of severe metabolic illnesses such as diabetes by early treatment when early indications are present.

The relationship of the survey films taken to the number of known cases and deaths for each year of the period 1946 to 1950 is shown in table 12. The decline of deaths cannot logically be attributed to the survey in this short period. Long-

TABLE 10

PROPOSED TABULAR METHOD FOR STUDYING SURVEY FINDINGS

A. The Follow-up of New Tuberculosis Patients Discovered in a Chest Roentgenographic Survey

PERIOD OF OBSERVATION (MONTHS)	TOTAL NUMBER (OF PATIENTS) UNDER STUDY AT BEGINNING OF STUDY PERIOD l_x	NUMBER OF PATIENTS LOST DURING PERIOD w_x	PERCENTAGE OF PATIENTS LOST $[w_x/l_x]$ 100	PREVIOUSLY LOST PATIENTS RETURNING DURING THE PERIOD n_x	NUMBER OF DEATHS DURING PERIOD d_x	PERCENTAGE OF PATIENTS DYING DURING PERIOD $[d_x/l_x]$ 100	NUMBER OF TUBERCULOSIS DEATHS DURING PERIOD $t_x d_x$	PERCENTAGE OF TUBERCULOSIS DEATHS DURING PERIOD $[t_x d_x/l_x]$ 100	PERCENTAGE UNDER STUDY BEGINNING OF PERIOD*
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
0 to 3									
3 to 6									
et cetera									

* First period = 100 per cent.

B. The Activity of Pulmonary Tuberculosis by Months of Observation

PERIOD OF OBSERVATION (MONTHS)	TOTAL UNDER STUDY AT BEGINNING OF STUDY PERIOD l_x	NUMBER DIAGNOSED ACTIVE DURING PERIOD a_x	PERCENTAGE DIAGNOSED ACTIVE $[a_x/l_x]$ 100	NUMBER DIAGNOSED QUESTIONABLY ACTIVE q_x	PERCENTAGE DIAGNOSED QUESTIONABLY ACTIVE $[q_x/l_x]$ 100	NUMBER DIAGNOSED ARRESTED $a r_x$	PERCENTAGE DIAGNOSED ARRESTED $[a r_x/l_x]$ 100	NUMBER DIAGNOSED INACTIVE i_x	PERCENTAGE DIAGNOSED INACTIVE $[i_x/l_x]$ 100
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
0 to 3									
4 to 6									
et cetera									

term projections of this chart are desirable. It is certainly evident that a larger number of annual survey films is required in the District of Columbia.

Persons diagnosed "definite tuberculosis" returned for study with greater certainty than those diagnosed "suspected," "positive pathology," or "negative tuberculosis follow." More patients respond to the request to return for extended follow-up if they *understand* the need for it. The importance of individual education of the diagnosed tuberculous patient in the meaning of his illness cannot, therefore, be stressed too strongly. The average patient is impressed only by symptoms or by definite statements from a physician.

Provision for individual patient instruction in the significance of asymptomatic tuberculous lesions of small extent, or indeed of all inactive or suspected

TABLE 11

PROPOSED TABULAR METHOD FOR STUDYING SURVEY FINDINGS

A. Disposition of Patients under Study by Facilities Responsible

PERIOD OF OBSERVATION (MONTHS)	TOTAL UNDER STUDY AT BEGINNING OF STUDY PERIOD	AMBULANT PUBLIC CLINICS	PERCENTAGE AMBULANT PUBLIC CLINICS	AMBULANT PRIVATE DOCTORS	PERCENTAGE AMBULANT PRIVATE DOCTORS	AWAITING HOSPITALIZATION	PERCENTAGE AWAITING HOSPITALIZATION	HOSPITALIZED TUBERCULOSIS	HOSPITALIZED OTHER	PERCENTAGE HOSPITALIZED	NOT STATED	PERCENTAGE NOT STATED
	$1x$	pcx	$[pcx/1x] \times 100$	pdx	$[pdx/1x] \times 100$	ahx	$[ahx/1x] \times 100$	htx	hox	$\frac{[htx + hox]}{1x} \times 100$	nsx	$[-nsx/1x] 100$
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
0 to 3												
3 to 6												
et cetera												

B. Sputum Status of Patients under Study by Period of Observation

PERIOD OF OBSERVATION (MONTHS)	TOTAL UNDER STUDY AT BEGINNING OF STUDY PERIOD	TOTAL NUMBER REPORTED POSITIVE ON ONE OR MORE SPUTUM EXAMINATIONS DURING PERIOD	PERCENTAGE REPORTED POSITIVE ON ONE OR MORE SPUTUM EXAMINATIONS	NUMBER REPORTED NEGATIVE ON THREE OR MORE EXAMINATIONS	PERCENTAGE REPORTED NEGATIVE ON THREE OR MORE EXAMINATIONS	NUMBER HAVING LESS THAN THREE NEGATIVE EXAMINATIONS OR NONE	PERCENTAGE HAVING LESS THAN THREE NEGATIVE EXAMINATIONS OR NONE
	$1x$	psx	$[psx/1x] 100$	nsx	$[nsx/1x] 100$	msx	$[msx/1x] 100$
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
0 to 3							
3 to 6							
et cetera							

TABLE 12

WASHINGTON, D. C., CHEST ROENTGENOGRAPHIC SURVEY FOLLOW-UP STUDY
THE NUMBER OF ROENTGENOGRAPHIC SURVEY FILMS, NEW CASES OF TUBERCULOSIS REPORTED, AND DEATHS FROM TUBERCULOSIS FROM 1946–1950, INCLUSIVE, WASHINGTON, D. C.

YEAR	MICROFILMS	CASES	DEATHS
1950	111,027	1,672	388
1949	105,573	1,591	440
1948	539,138	5,263	470
1947	83,105	1,859	529
1946	97,218	2,288	525

tuberculosis, is a great need which has grown out of mass survey examinations. This can be provided only by giving both clinic physicians and nurses the time to give each patient the full explanation he deserves.

Again, the medical study of the entire patient is essential. The effect of metabolic diseases and chronic alcoholism upon previously inactive tuberculosis is well known. It would seem more logical to label an apparently inactive tuberculous lesion in a diabetic, alcoholic, or nephrotic as "potentially active tuberculosis" because of concomitant illness than to leave the future activity of the lesion to speculation.

Figure 5 is a diagram which postulates the reservoir of tuberculosis in the community.

Although a number of new infections must develop immediately after contact and become active and the patient become clinically ill immediately, the follow-

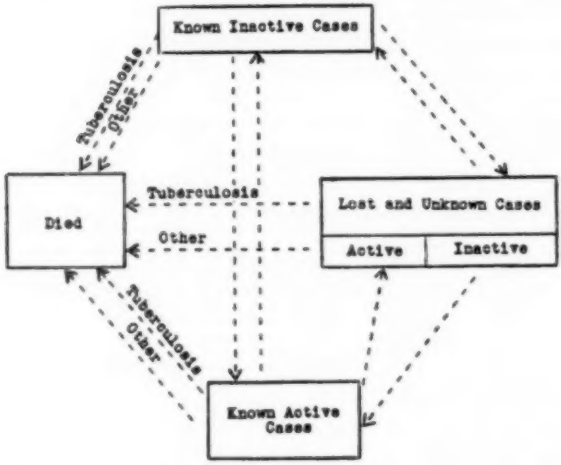

FIG. 5. A scheme representing the possible change of status among tuberculosis patients in a community.

up studies seem to indicate that a number of inactive lesions and asymptomatic patients exist at all times in the community. Other studies indicate that new cases may develop in a given group of roentgenographically negative persons within a very short time (2). This study seems to indicate that a number of persons with unrecognized inactive tuberculosis are potentially progressive.

The reservoir of inactive and arrested cases present at any time in the community constantly changes with the passage of time. Approximately one-half are known at any one time. There exists also a group of "lost or unknown cases," both inactive and active. The group of known active cases of tuberculosis in the present study is proportionately small. The reservoir of "potentially active" tuberculosis requires attention.

In order to make the early diagnosis of tuberculosis significant, a way must be

found to keep the greatest possible number of persons with known inactive lesions from moving either into the "known active group" or into the "unknown active group" where they may become unrecognized spreaders and contribute to the development of new tuberculosis cases. The success with which this is done may be a measure of the significance of early diagnosis.

The survey indicated that concerted efforts are required to bring about an organized and well-directed control of tuberculosis. Although it was not possible to show the number of additional patient-months of hospitalization made necessary by the survey, it is known that additional beds were provided. The need for an increased number of hospital beds is indicated by the relatively large probability of death for patients with far advanced disease (23.73 per cent) discovered at the time. The large number (704) of patients who did not receive exact diagnoses and the 534 in whom the activity of the disease was not stated showed a relatively large probability of death (3.88 per cent and 5.00 per cent). Should these patients have been hospitalized? The probability of their disease worsening suggests a similarity to the group with moderately advanced or active disease.

The probability of an unfavorable change in conditions in twenty-four months indicated by table 8 for "inactive" and "activity unknown" patients is 17.76 per cent. More accurate methods of determining activity, if available, would undoubtedly require an increased number of hospital beds or the development of facilities for ambulant therapy.

Adequate facilities for treatment are not available either in District hospitals or in the clinics, and an attempt should be made to institute the following measures:

More annual small film examinations are needed in order to recognize a larger proportion of the tuberculosis cases, particularly in older persons.

Well-staffed and organized clinical and laboratory facilities are required in order to determine with the accuracy possible by full use of modern methods whether or not tuberculous lesions are presently active, potentially active in later years, or truly obsolete.

Clinical teaching of patients by physicians and nurses should be extended from instruction in curative procedures and immediate prophylaxis to teaching intended to prevent the development of progressive tuberculosis.

The aid of the geriatrist, the internist, and the practioner is required to ensure that a maximum of general health is maintained in the face of inactive tuberculosis.

The nursing follow-up of tuberculosis must be more extensive and increasingly directed to keeping the patient with "inactive" tuberculosis under medical observation.

The public chest clinics, which in Washington carry the major burden of supervision and medical care for tuberculous patients, should be adequately staffed in order to allow sufficient time for the physicians to study the entire patient, as well as his roentgenograms. Patients must be taught the meaning of their medical findings.

Modern facilities for the bacteriologic study of body secretions of tuberculous

patients should be made available to the clinics. Too few examinations for the presence of tubercle bacilli render activity determinations prolonged and costly.

An interpretation by a radiologist assigned to chest clinics added to the final roentgenographic interpretation of the clinic physician would increase the accuracy of radiologic studies.

The educational program in the community should teach the need for roentgenographic examination of the entire population. The patient must be taught the importance of preventing tuberculous illness by proper medical observation of inactive or minor pulmonary lesions.

The distinction between "progressive-possibily-fatal-tuberculosis with contagion" and "inactive-noncontagious-tuberculosis potentially dangerous later" must be stressed.

The possibility that social services and vocational rehabilitation, if available to patients discovered in surveys, might avert tuberculosis progression by ameliorating social and economic stresses and preventing physical overstrain in unsuitable employment requires careful study. The use of these facilities in a preventive way seems to make good medical sense and should result in real economies.

SUMMARY

The effects of the chest roentgenographic survey upon the community are not entirely measurable. It is generally agreed that the benefits of the intensive program of public education cannot be calculated. In the present survey of the District of Columbia, more physicians sought chest films for their patients; more patients requested them.

The total effect of the survey upon the hospitals was not evident. It is certain that more beds are needed than are now available in order to place more of the active patients under treatment and care. The number of beds available influences the recommendations of physicians for hospitalization. Although the hospital waiting list did not increase during the survey, many patients with active tuberculosis were retained on ambulant care.

The prevalence of tuberculosis discovered in patients 55 years of age and older is a challenge to educational and case-finding skill.

The probability that the survey plus all other measures disclosed only two-thirds of the cases of tuberculosis in Washington, D. C., in 1948 points up the need for continued intensive case finding.

The follow-up study showed the need for improvement of clinic facilities, more public health nursing follow-up, and better clinical laboratory facilities.

The probability of previously unknown patients surviving under the conditions of care existing in the District of Columbia in the thirty months after January, 1948, was 97.52 per cent. The probability of patients diagnosed "inactive tuberculosis" becoming worse was almost 10 per cent .

A tabulation is proposed for the follow-up of cases discovered in surveys in order that a uniform standard of comparison may be developed upon which to base an analysis of facilities.

SUMARIO

Estudio de los Hallazgos Radiográficos Positivos de la Encuesta Colectiva de 1948 en Wáshington: Estado a los Dos Años

No cabe medir del todo los efectos de las encuestas radiográficas del tórax sobre la colectividad. La mayoría de nosotros ya convenimos en que no pueden calcularse los beneficios derivados del programa intenso de educación del público. Más médicos solicitaron radiografías torácicas para sus clientes, más enfermos las solicitaron.

El efecto total de la encuesta sobre los hospitales no fué evidente. Es un hecho que se necesitan más camas que las disponibles actualmente a fin de ofrecer tratamiento y asistencia a más enfermos de los activos. El número de lechos disponibles afecta las recomendaciones de los médicos en cuanto a hospitalización. Aunque no aumentó durante la encuesta la lista de candidatos a camas, se retuvo en asistencia ambulante a muchos enfermos con tuberculosis activa.

La frecuencia de tuberculosis descubierta en enfermos de cincuenta y cinco años o más de edad constituye un reto a nuestra destreza educativa y pesquisadora.

La probabilidad de que la encuesta, unida a todas las demás providencias, no revelara más de dos terceras partes de los casos de tuberculosis existentes en la ciudad en 1948 señala la necesidad de de continuas e intensas pesquisas de casos.

El estudio subsiguiente demostró la necesidad de mejorar los recursos en clínicas, de más atención subsiguiente por enfermeras sanitarias y de mejorar los medios de laboratorio clínico.

La probabilidad de que enfermos antes desconocidos sobrevivan en las condiciones de asistencia que han existido en el Distrito de Columbia en los treinta meses transcurridos desde enero de 1948, es de 97.52 por ciento. La probabilidad de que hayan empeorado enfermos diagnosticados como con "tuberculosis inactiva" representa casi 10 por ciento.

RESUME

Une étude des résultats radiographiques positifs des examens collectifs de 1948 à Washington

Les effets de cette enquête municipale fondée sur des examens radiographiques collectifs du poumon ne peuvent être évalués avec précision. La plupart des auteurs admet que les avantages d'un programme intensif d'éducation de public sont incalculables. Le nombre de médecins réclamant des clichés du poumon pour leurs malades et le nombre de malades qui les demandent est de plus en plus grand.

L'effet complet de cette enquête, en ce qui concerne le problème hospitalier, n'a pas été démontré. Il est certain qu'il faut un nombre de lits plus grand que celui dont on dispose actuellement, pour y placer les cas en activité qui réclament un traitement et des soins. Le nombre de lits disponibles influence la prescription de l'hospitalisation par les médecins. Bien que la liste d'attente pour l'admission à l'hôpital ne se soit pas accrue au cours de l'enquête, beaucoup de malades affectés de tuberculose en activité continuent à recevoir un traitement ambulatoire.

La prédominance de la tuberculose découverte chez des malades agés de cinquante ans, et plus, constitue un défi à l'égard de nos méthodes d'éducation du public et à notre capacité de déceler les cas de tuberculose.

Selon les probabilités, cette enquête et l'ensemble des mesures prises n'ont permis de découvrir que les deux tiers des cas de tuberculose dans cette ville en 1948, ce qui montre la nécessité de poursuivre avec vigueur les travaux pour la recherche des cas de tuberculose.

La suite des observations a montré le besoin d'une amélioration des facilités offertes par les dispensaires, de l'augmentation des services d'hygiène publique chargés de poursuivre l'observation des cas et d'offrir des facilités pour les examens de laboratoire en clinique.

Les probabilités indiquent que la proportion des malades, antérieurement non identifiés, qui survivent dans les conditions de soins dispensés par le "District of Colombia"

(Washington) dans les trente mois qui ont suivis le mois de janvier 1948, est de 97,52%. La proportion des malades pour lesquels la diagnostic de "tuberculose inactive" avait été posé, et dont l'état s'est aggravé, est évaluée à presque 10%.

Acknowledgment

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EFFECTS OF THE COMPOSITION OF THE MEDIUM ON THE GROWTH, MORPHOLOGY, AND VIRULENCE OF MYCOBACTERIUM TUBERCULOSIS VAR. AVIUM[1]

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INTRODUCTION

Many of the properties of the bacterial cell are influenced by the composition of the medium. The form, size, and enzyme content of the cell and the products of fermentation are properties which may be profoundly modified by changes in the composition of the medium. It is also known that the action of certain chemotherapeutic agents is explainable by their effect on the metabolism of the pathogen and a consequent decrease in its virulence.

In the present work, a study has been made of the effect of changes in the composition of the medium on the general morphology, acid-fastness, and virulence of *Mycobacterium tuberculosis*. In the study of virulence, it is realized that the bacterial cells might not retain the characteristics observed *in vitro* when inoculated into the animal body and that during their multiplication *in vivo* they might gradually reacquire their normal properties. This would undoubtedly require time, however, and it is reasonable to expect that any effect on virulence resulting from growth in the artificial media used would be detectable in the animal.

MATERIALS AND METHODS

Strain and Media

The strain of *Mycobacterium tuberculosis* used in the investigation was the Sheard strain of the avian variety, obtained from the Trudeau Sanatorium, Saranac Lake, New York, through the courtesy of Mr. W. Steenken, Jr. The cytology of this strain has recently been studied by Knaysi, Hillier, and Fabricant (1).

Stock cultures of the organism were grown on Dorset's egg medium, and in a few experiments Besredka's egg-yolk medium was used to obtain diffuse growth and study the effect of varying the concentration of egg yolk on the size of clumps. In most of the experimental work, however, one of the media of *Dubos* and his associates[2] (2) was used, and it was by varying the composition of this medium that the effect of composition of the medium on acid-fastness and virulence was studied. Henceforth, this medium will be referred to as *medium D*.

Medium D was modified either by reducing the concentration of some of its minerals or

[1] From the Laboratory of Bacteriology, State College of Agriculture, and the Department of Pathology and Bacteriology, New York State Veterinary College, Cornell University, Ithaca, New York.

[2] This medium has the following composition: $Na_2HPO_4 \cdot 12H_2O$, 6.3 gm.; KH_2PO_4, 1.0 gm.; $MgSO_4 \cdot 7H_2O$, 0.6 gm.; asparagine, 1 gm.; Na citrate. $2H_2O$, 1.5 gm.; ferric ammonium citrate, 0.1 gm.; ester of Sorbitan monooleate (Tween 80), 0.5 ml.; q.s. distilled water to make 1,000 ml. of medium.

by the addition of a new component to produce: *medium* D_1, in which the concentrations of sodium and potassium phosphates and of magnesium sulfate were reduced to 0.1 of their value in D; D_2, in which the phosphates were reduced to 0.01 and the sulfate to 0.1 of their value in D; D_3, in which both the phosphates and sulfate were reduced to 0.01 of their value in D. New components added to D were penicillin, barbituric acid, or benzimidazole. These substances are known to influence the course of metabolism, particularly nucleic acid metabolism.

The preparation of *medium D* and of its derivatives was simplified by preparing stock solutions of their components. Most of these solutions were kept in glass-stoppered bottles at room temperature; stock solutions of Tween[1] and of asparagine were kept in the refrigerator. Whenever turbidity was observed in a stock solution, the solution was discarded and a fresh one prepared.

All glassware was cleaned with dichromate-sulfuric acid cleaning solution and subsequently rinsed eight times with tap water and six times with distilled water. The media were sterilized in 250 ml., Pyrex, Erlenmeyer flasks plugged with aluminum foil stuffed with cotton. The purpose of the aluminum foil was to reduce to a minimum the inhibitory action of volatile oils from the cotton. A four-inch square foil was so wrapped as to cover completely the rim of the flask.

The media thus prepared were distributed in Pyrex glass tubes, 25 mm. in internal diameter. The tubes received 5 ml. each by means of pipettes which were sterilized unplugged in copper cans and were plugged with sterile cotton just before use.

RESULTS

Experiments in Vitro

Purpose and procedure: The purpose of the experiments *in vitro* was to study the morphologic and cultural changes induced by changes in the composition of the medium and to serve as a guide in the selection of media and cultural stages to be used in the tests of virulence.

The technique involved in these studies was principally that of counting the total number of acid-fast and nonacid-fast cells in suspensions prepared from cultures at various time intervals during cultural development. Total numbers were determined by a modification of the cover-glass technique of Knaysi and Ford (3). One-hundredth of a milliliter of culture was deposited on a clean slide by means of a loop known to deliver that amount. This droplet of culture was covered with a square cover glass, 1.2 by 1.2 mm. The edges of the cover glass were sealed with vaspar, a mixture of equal parts of vaseline and paraffin. Since the volume of the droplet and the area of the cover glass were known, the depth of the liquid film under the cover glass could be readily calculated. As the area of a microscopic field and the fraction of ml. covered by the microscopic field were known, the number of cells per ml. could also be readily calculated.

The numbers of acid-fast and nonacid-fast cells were determined in smears stained by the Ziehl-Neelsen method (4). An area of one square centimeter, marked on a clean glass slide, was covered with 0.01 $cm.^2$ of culture properly diluted with 0.001 per cent solution of egg albumin. As in the case of the total counts, this volume was also measured with a standardized loop. The smear was then air-dried under a bell jar at 37°C., fixed by heat, and stained. The purpose of the egg albumin was to make the smear adhere to the slide more firmly and thus reduce the number of cells lost during the staining procedure.

The staining procedure was as follows: The slide carrying the smear was flooded with

[1] Tween 80 is the proprietary name for polyoxyethylene derivative of Sorbitan monooleate, obtained from the Atlas Powder Co., Wilmington, Delaware.

Ziehl-Neelsen's solution and heated with a Bunsen burner until steam became noticeable. Heating was then discontinued until the steam was no longer visible. This was repeated for five minutes. The slide was then dipped consecutively in four Coplin jars containing 3 per cent hydrochloric acid in 95 per cent ethyl alcohol, again rinsed with distilled water, allowed to drain for ten seconds, and counterstained with an aqueous solution of methylene blue. In the early stages of the investigation, Löffler's methylene blue was used as a counterstain, but the use of this solution was discontinued to avoid the effect of metachromatism. The counterstain was rinsed off with water, and the slides were allowed to drain over paper towels until dry. Counts made on such smears were generally in fair agreement with those made by the more trustworthy cover-glass method.

All cultures used for quantitative work were inoculated with a known number of cells and, before counting or diluting, the growth was dispersed by shaking the tube manually. Mechanical shaking was discontinued when it was found that it affected the number of acid-fast cells and, probably, the virulence.

Growth in the medium D: In young cultures, growth of the organism in *medium D* was diffuse, consisting of single cells and groups that seldom exceeded 10 cells. In cultures of six days or more, clumps of 10 to 20 cells were common. The presence of clumps made counting of the population difficult. The individual cells were longer than those grown on Dorset's egg medium and, stained or unstained, they appeared beaded; in cultures grown on the egg medium, beading was infrequent.

In most of the experiments, the maximum population in *medium* D_1 was considerably higher than in *medium D* (table 1), often by a factor of 2 to 2.5. In media D_2 and D_3, the maximum population was sometimes slightly lower than in D (table 1), but in several experiments it was higher, up to a factor of approximately 1.5.

In all media, D to D_3, nonacid-fast cells were observed. The proportion of these cells reached a maximum in cultures two to five days old. They were most commonly present in cultures four days old, a period which was still during the phase of cultural growth.

Effect of certain substances on the growth and properties of the cells: The effects of penicillin, barbituric acid, or benzimidazole were tested in *medium D*. One thousand units of penicillin per ml. of the medium markedly reduced the maximum population. This reduction was noted whether the penicillin was added at the time of inoculation or seventy-two hours after inoculation. The cells were also one-half to one-third as long as those of the control medium, and many had coccal forms. Penicillin also increased the maximum proportion of nonacid-fast cells (table 1).

Barbituric acid in the concentration of 2 mg. per ml. of medium reduced the maximum population; lower concentrations had an initial depressing effect that later disappeared. Barbituric acid also increased the maximum proportion of nonacid-fast cells. In the presence of 2 mg. per ml., the maximum proportion of nonacid-fast cells was reached in four to six days, apparently at the same stage of cultural development in which a maximum is reached in control cultures (table 2).

The effect of benzimidazole was similar to that of barbituric acid but was more pronounced and persistent. In cultures four to six days old and containing

TABLE 1

THE CHANGE IN TOTAL POPULATION AND IN THE PROPORTION OF ACID-FAST CELLS DURING CULTURAL DEVELOPMENT IN MEDIA D TO D_3, AND IN THESE MEDIA PLUS 1,000 UNITS OF CRYSTALLINE PENICILLIN PER MILLILITER

MEDIUM	AGE OF CULTURE	CULTURES WITHOUT PENICILLIN		CULTURES CONTAINING 10^3 UNITS OF PENICILLIN PER ML.	
		Number of Cells.* Cover Glass Method	Per Cent of Nonacid-fast Cells	Number of Cells* Cover Glass Method	Per Cent of Nonacid-fast Cells
	days				
D	2	5,680	25.8	2,556	92.8
	4	63,900	37.2	2,276	58.3
	6	75,850	27.0	1,420	75.9
	9	46,860	5.8	710	71.0
	13	35,500	9.8	1,122	100.0
D_1	2	4,260	45.3	1,420	87.4
	4	112,180	42.5	1,420	64.6
	6	95,140	28.6	1,420	72.7
	9	49,700	18.0	994	77.7
	13	24,140	29.8	3,003	100.0
D_2	2	3,692	32.5	1,846	100.0
	4	32,660	50.6	994	88.8
	6	29,650	18.8	1,420	90.9
	9	41,840	9.6	426	87.0
	13	22,070	8.9	2,414	100.0
D_3	2	4,260	46.2	1,420	95.8
	4	55,250	39.4	1,562	71.0
	6	31,250	33.3	1,136	100.0
	9	32,660	4.0	1,026	66.7
	13	30,360	12.5	3,384	50.0

* Each count represents the number of cells per ml. of culture and should be multiplied by 1,000.

TABLE 2

CHANGE IN TOTAL POPULATION AND IN THE PROPORTION OF ACID-FAST CELLS DURING CULTURAL DEVELOPMENT IN MEDIUM D CONTAINING 0.002 GM. OF BARBITURIC ACID OR BENZIMIDAZOLE PER MILLILITER

AGE OF CULTURE	CONTROL		0.002 GM. BARBITURIC ACID		0.002 GM. BENZIMIDAZOLE	
	Total Cells*	Per cent of Nonacid-fast Cells	Total Cells*	Per cent of Nonacid-fast Cells	Total Cells*	Per cent of Nonacid-fast Cells
days						
2	4,899	33.2	2,506	36.5	3,408	38.8
4	26,980	40.0	4,970	98.7	3,550	99.0
6	42,600	28.6	6,390	77.0	4,086	96.6
8	106,210	14.8	11,928	39.8	5,964	61.0
10	160,460	2.3	31,240	69.0	9,940	75.8
12	103,660	19.0	71,710	43.9	2,110	69.4
16	54,160	15.8	34,790	42.8	1,278	64.4

* Each count represents the number of cells per ml. of culture and should be multiplied by 1,000.

1 to 2 mg. of benzimidazole per ml., more than 90 per cent of the cells were nonacid-fast. Moreover, the proportion of nonacid-fast cells continued to be much higher than in the control medium for as long as sixteen days. In the absence of benzimidazole, the proportion of nonacid-fast cells seldom exceeded 40 per cent. These data confirm those of Knaysi, Hillier, and Fabricant (1).

Effect of shaking: Mechanical shaking of the culture increased the proportion of nonacid-fast cells. In one experiment, a culture was divided into two portions; one portion was stained without previous shaking and the other was shaken mechanically for twenty minutes at low speed. It was found that this mild shaking increased the proportion of nonacid-fast cells from 9.8 to 23 per cent.

Experiments in Vivo

Procedure: Details of the technique of growing the cultures used for inoculating the experimental animals were similar to those described for the experiments *in vitro*.

The animals employed in all experiments were single-combed, white Leghorn chickens (cockerels and pullets) seven weeks old. These chickens came from a flock known to be free of tuberculosis. The birds were placed in battery cages, not more than 9 birds per deck, and were held at least three days before inoculation. They were fed commercial, pelleted growing-mash, and fresh water was kept before the birds at all times. The experiments usually lasted seven to nine weeks.

The birds were inoculated into the brachial vein with varying numbers of cells of the *Mycobacterium* from cultures usually grown in *medium D* or one of its modifications. Prior to inoculation, the cultures were shaken manually approximately twenty-five times and the number of cells per ml. was determined. Then serial dilutions were made with 0.8 per cent sodium chloride solutions. The dilutions were such that 1 ml. of suspension would contain the number of cells to be injected. Attempts to disperse the cells by mechanical means were avoided when it was suspected that these methods, besides increasing the proportion of nonacid-fast cells, reduced virulence. All dilutions and counts were made just prior to inoculations.

The batteries housing the birds were cleaned two or three times a week. After inoculation, daily observation was made of the physical appearance of the birds and the amount of food they consumed. In each group one bird was killed and autopsied six weeks after inoculation; the remainder were killed and autopsied seven weeks after inoculation. Killing was accomplished by breaking the spinal cord in the neck region.

All internal organs were examined for lesions of tuberculosis. Smears were made of all suspicious lesions and stained by the Ziehl-Neelsen method as described in the preceding section.

In the interpretation of the results, it was decided to judge the virulence of the organisms solely on the basis of the number and character of the gross lesions. The presence of diffuse lesions only was interpreted as an indication of *high virulence*, and the presence of discrete lesions only was considered to mean *low virulence*. It is evident that several degrees of low virulence would be found, depending upon the number of discrete lesions and the extent of involvement of internal organs. A change in virulence was recognized by comparing the severity of the disease in birds inoculated with the same number of cells from different cultures.

The distribution of lesions was characteristic of that resulting from the intra-

venous administration of avian tubercle bacilli to the chicken, as has been described by others. Gross lesions were found uniformly in the spleen, liver, and bone marrow. Because of the difficulty of making uniform examinations of the bone marrow, only the liver and spleen were used in the evaluation of gross lesions. To simplify evaluation and comparison of the gross lesions, an arbitrary standard or index of virulence was set up:

1 to 5 lesions expressed as 1
6 to 25 lesions expressed as 2
26 to 100 lesions expressed as 3
101 to 200 lesions expressed as 4
Miliary or diffuse lesions expressed as 5

The spleen and liver were evaluated separately on this scale. The sum of the values of the liver and the spleen constituted the index of virulence for the bird. Thus, a range from 0 to a maximum value of 10 was possible for this value.

Observations on virulence: Infection was obtained when as few as 10 cells were injected intravenously. The reactions of the various birds to inoculation were generally similar; one or two days after inoculation they appeared somewhat "droopy", with ruffled feathers and loss of appetite. In three to four days this initial reaction was followed by an apparent recovery that lasted several days. At the end of one week to ten days the birds again began to look "droopy", with ruffled feathers and loss of appetite. This second reaction to the inoculation was not followed by recovery. Birds which received the low doses (10 to 10^5 cells) appeared to be in a better condition throughout the experiments than birds which received the higher doses.

Lesions were found most frequently in the liver and spleen and, occasionally, in the lung and myocardium. In contrast with the natural disease in chickens, in which the normal route of infection is via the gastrointestinal tract, no lesions were found in the intestinal tract. This probably explains the fact that, in experiments when control and infected birds were placed together in the same cages, the controls did not contract tuberculosis during the course of the experiments.

On the basis of three experiments involving 9 birds for each number of cells injected, it may be stated that reduction of the concentrations of phosphates and sulfate to 0.01 of their value in *medium D* (*medium* D_2) appears to result in a definite reduction in virulence (tables 4 and 5). Reduction of the concentrations of the phosphates and sulfate to 0.1 (*medium* D_1) or of the phosphates to 0.01 and the sulfate to 0.1 (*medium* D_2) of their original values in *D* appears also to cause reduction in virulence, although the true extent of reduction here may differ from the results of the single experiments recorded in table 3.

Following the observations of Knaysi, Hillier, and Fabricant (1) that the addition of 0.001 gm. of benzimidazole per ml. of culture medium rendered the cells nonacid-fast, it seemed desirable to find out whether or not the virulence of the organism is also affected by the loss of acid-fastness. It is shown in table 6 that, although in the majority of cases there is a definite reduction in the index of virulence, yet as few as 10 of the nonacid-fast cells can cause infection in most birds.

TABLE 3

VIRULENCE OF CULTURES GROWN ON DORSET'S EGG MEDIUM, MEDIUM D_1, AND MEDIUM D_2, AND INOCULATED INTO SEVEN-WEEK-OLD CHICKENS

NUMBER OF CELLS INJECTED	DORSET'S EGG MEDIUM		MEDIUM D_1		MEDIUM D_2	
	Range of Index of Virulence of Individual Birds	Average Index of Virulence for Dilution	Range of Index of Virulence of Individual Birds	Average Index of Virulence for Dilution	Range of Index of Virulence of Individual Birds	Average Index of Virulence for Dilution
10	2	2.0	1–4	3.0	0–1	0.6
10^2	2	2.0	2–4	2.6	1	1.0
10^3	1–2	1.7	2–4	2.6	0	0.0
10^4	4	4.0	2–4	3.3	1–2	1.3
10^5	2–4	3.3	2–4	3.3	1	1.0
10^6	4	4.0	4–6	5.0	1	1.0
10^7	8–10	8.7	8–10	9.3	1	1.0

TABLE 4

VIRULENCE OF CULTURES GROWN ON MEDIUM D AND INOCULATED INTO SEVEN-WEEK-OLD CHICKENS. SUMMARY OF THREE TRIALS

NUMBER OF CELLS INJECTED	TRIAL NUMBER	RANGE OF INDEX OF VIRULENCE OF INDIVIDUAL BIRDS	AVERAGE INDEX OF VIRULENCE FOR TRIAL	AVERAGE INDEX OF VIRULENCE FOR DILUTION
10	A	4	4.0	3.0
	B	4	4.0	
	C	0–2	1.0	
10^2	A	4	4.0	2.9
	B	0–4	2.7	
	C	0–4	2.0	
10^3	A	4	4.0	4.7
	B	5–6	5.7	
	C	4–5	4.3	
10^4	A	4–8	6.0	5.2
	B	5–6	5.3	
	C	3–5	4.3	
10^5	A	8	8.0	7.8
	B	6–8	6.6	
	C	6–10	8.6	
10^6	A	6–10	9.3	9.3
	B	8–10	8.6	
	C	10	10.0	
10^7	A	4–10	8.0	9.0
	B	8–10	9.3	
	C	9–10	9.6	

In table 7 the data on virulence recorded in tables 3 to 6 have been brought together.

It must be stressed that these observations on virulence are of limited significance because of the great variation in results in repeated trials of the same culture. As great a variation was sometimes seen within different trials of the same culture as was seen between different cultures.

TABLE 5

VIRULENCE OF CULTURES GROWN ON MEDIUM D_1 AND INOCULATED INTO SEVEN-WEEK-OLD CHICKENS. SUMMARY OF THREE TRIALS

NUMBER OF CELLS INJECTED	TRIAL NUMBER	RANGE OF INDEX OF VIRULENCE OF INDIVIDUAL BIRDS	AVERAGE INDEX OF VIRULENCE FOR TRIAL	AVERAGE INDEX OF VIRULENCE OF DILUTION
10	A	0-1	0.3	1.2
	B	1	1.0	
	C	1-3	2.3	
10^2	A	1	1.0	1.7
	B	1-3	2.0	
	C	0-3	2.0	
10^3	A	0-1	0.3	1.3
	B	0-4	1.6	
	C	1-3	2.0	
10^4	A	1	1.0	2.5
	B	3-4	3.6	
	C	2-4	3.0	
10^5	A	0-1	0.3	3.9
	B	1-6	3.6	
	C	6-9	7.6	
10^6	A	1	1.0	5.9
	B	7-10	8.3	
	C	7-10	8.0	
10^7	A	0-1	0.6	6.8
	B	9-10	9.6	
	C	10	10.0	

SUMMARY

When the Sheard strain of *Mycobacterium tuberculosis* var. *avium* is grown in *medium D*, a synthetic medium developed by Dubos and his co-workers (1946), the bacterial cells grow throughout the medium in clumps of various sizes which seldom exceed 10 cells per clump in young cultures. In cultures more than six days old, clumps of 10 to 20 cells are common. Cultures grown in this medium are highly virulent. Reducing the concentration of sodium and potassium phosphates and of magnesium sulfate to 0.1 of their original values results in an in-

TABLE 6

VIRULENCE OF CULTURES GROWN ON MEDIUM D PLUS 0.001 GM. OF BENZIMIDAZOLE PER ML. AND INOCULATED INTO SEVEN-WEEK-OLD CHICKENS. SUMMARY OF THREE TRIALS

NUMBER OF CELLS INJECTED	TRIAL NUMBER	RANGE OF INDEX OF VIRULENCE OF INDIVIDUAL BIRDS	AVERAGE INDEX OF VIRULENCE FOR TRIAL	AVERAGE INDEX OF VIRULENCE FOR DILUTION
10	A	2-4	3.3	1.8
	B	1	1.0	
	C	0-2	1.0	
10^2	A	4-5	4.3	4.2
	B	2-3	2.3	
	C	2-10	6.0	
10^3	A	4-5	4.3	2.6
	B	1-3	2.0	
	C	0-3	1.3	
10^4	A	5	5.0	3.0
	B	3	3.0	
	C	0-2	1.0	
10^5	A	7-8	7.3	4.3
	B	1-5	3.3	
	C	2-3	2.3	
10^6	A	10	10.0	4.2
	B	1-4	2.0	
	C	0-1	0.3	
10^7	A	10	10.0	4.9
	B	2-5	3.3	
	C	0-2	1.3	

TABLE 7

COMPARISON OF AVERAGE INDEX OF VIRULENCE OF CULTURES GROWN ON VARIOUS MEDIA (SUMMARY OF TABLES 3 TO 6)

MEDIUM	NUMBER OF TRIALS	NUMBER OF CELLS INJECTED							GRAND AVERAGE
		10	10^2	10^3	10^4	10^5	10^6	10^7	
Dorset's egg medium	1	2.0	2.0	1.7	4.0	3.3	4.0	8.7	3.7
D	3	3.0	2.9	4.7	5.2	7.8	9.3	9.0	5.6
D_1	1	3.0	2.6	2.6	3.3	3.3	5.0	9.3	4.2
D_2	1	0.6	1.0	0.0	1.3	1.0	1.0	1.0	0.9
D_3	3	1.2	1.7	1.3	2.5	3.9	5.9	6.8	3.4
D plus 0.001 gm. of Benzimidazole per ml	3	1.8	4.2	2.6	3.0	4.3	4.2	4.9	3.6

crease in the maximum number of cells, often to more than twice the value in the unchanged medium and in apparent reduction in the virulence of the culture. Further reduction in the concentration of the phosphates or of the phosphates and the sulfate to 0.01 of their original values gives a maximum population comparable to that found in *medium D*, but the cultures seem to be of lower virulence.

All cultures in *medium D* and its derivatives have a certain proportion of nonacid-fast cells which reaches a maximum some time before the end of the phase of cultural growth. The addition of 0.001 gm. of barbituric acid or of benzimidazole per ml. raises this maximum to almost unity. The nonacid-fast cells formed in the presence of benzimidazole are virulent, although the degree of their virulence is somewhat below that of cultures grown in *medium D*.

Mechanical shaking for twenty minutes or more results in an increase in the proportion of nonacid-fast cells.

SUMARIO

Efecto de la Composición del Medio sobre el Desarrollo, Morfología y Virulencia del Mycobacterium Tuberculosis var. Avium

Cuando se cultiva la cepa Sheard del *Mycobacterium tuberculosis* var. *Avium* en el medio D, medio este sintético elaborado por Dubos y colaboradores (1946), prolifera por todo el medio en grupillos de varios tamaños, pero rara vez excediendo de 10 células por grupo en los cultivos jóvenes. En los cultivos de más de seis días, los grupos de 10 a 20 células son frecuentes. Los cultivos criados en dicho medio son muy virulentos. La baja de la concentración de los fosfatos de sodio y de potasio y del sulfato de magnesio a 0.1 de las cifras primitivas da por resultado un aumento del número máximo de células, a menudo a más del doble que en el medio inalterado, y una disminución aparente de la virulencia del cultivo. Otra reducción de la concentración de los fosfatos o de éstos y del sulfato a 0.01 de las cifras primitivas obtiene una población máxima comparable a la observada en el medio D, pero los cultivos parecen ser menos virulentos.

Todos los cultivos en el medio D y en los derivados del mismo contienen cierta proporción de células anacidorresistentes que alcanza su máximo algo antes de terminar la fase de desarrollo cultural. La adición de 0.001 gm. por ml. de ácido barbitúrico o de bencimidazol eleva dicho máximo casi a la unidad. Las células anacidorresistentes formadas en presencia de bencimidazol son virulentas, aunque la virulencia de las mismas es algo inferior a la de los cultivos criados en el medio D.

La agitación mecánica durante veinte minutos o más hace subir la proporción de células anacidorresistentes.

RESUME

Effet de la composition du milieu de culture sur la croissance, la morphologie et la virulence du Mycobacterium tuberculosis var. Avium

Quand la souche Sheard du *Mycobacterium tuberculosis* var. *Avium* est cultivée dans le milieu synthétique élaboré par Dubos et ses collaborateurs (1946), il pousse en colonies de dimensions variées; dans les cultures jeunes il y a rarement plus de 10 cellules par colonies. Dans les cultures ayant plus de six jours, les colonies de 10 à 20 cellules sont habituelles. Les cultures développées dans ce milieu de culture sont très virulentes. La réduction de la concentration des phosphates de sodium et de potassium et du sulfate de magnésium, au 1/10ème de leur valeur originale, détermine une augmentation du nombre maximum de

cellules, dépassant souvent le double de sa valeur dans le milieu non modifié, ainsi qu'une réduction manifeste de la virulence de la culture. Une réduction plus marquée dans la concentration des phosphates ou des phosphates et des sulfates, au 1/100ème de leur valeur originale, donne un nombre maximum de cellules comparable à celui du milieu D, mais les cultures semblent douées d'une moindre virulence.

Toutes les cultures du milieu D et de ses dérivés comportent une certaine proportion de cellules non acido-résistantes, qui atteint son maximum dans la période précédant la fin de la phase de la croissance de la culture. L'addition d'acide barbiturique ou de benzimidazole dans la proportion de 0.001 g. par ml. élève ce maximum à presque l'unité. Les cellules non acido-résistantes formées en présence de benzimidazole sont virulentes, bien que le degré de leur virulence soit légèrement inférieur à celui des cultures développées sur le milieu D.

L'agitation mécanique pendant vingt minutes, ou plus, a pour résultat l'accroissement de la proportion des cellules non acido-résistantes.

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THE ISOLATION OF HISTOPLASMA CAPSULATUM FROM SPUTUM[1]

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INTRODUCTION

The pulmonary manifestations of histoplasmosis have been the subject of many reports in recent years and apparently represent a common type of pulmonary disease in certain areas of the United States. Nevertheless, demonstration of *Histoplasma capsulatum* in sputum is relatively infrequent, and the few reports of successful isolation have come from sources where hospitalized patients were under study for undiagnosed pulmonary disease.

The present writer has cultured several hundred sputum specimens from suspected cases for *H. capsulatum* and, until recently, has been unsuccessful. The majority of these specimens were from patients seen in the outpatient clinic, many of whom had negative tuberculin and positive histoplasmin skin reactions (1). The specimens were mailed in and, consequently, several days elapsed before the sputum was cultured.

In view of the infrequency with which *H. capsulatum* has been recovered from expectorated material, an evaluation was made of the methods used in the isolation of this fungus from sputum. In addition, detailed studies on the morphology and growth characteristics of this organism are included as an aid to ready identification.

EXPERIMENTAL METHODS AND RESULTS

The fact that *H. capsulatum* has been recovered from the sputum of but a small percentage of patients with other findings indicative of histoplasmosis suggested the possibility that these organisms might remain viable for only a short period of time in sputum. To this end, a series of experiments was planned to determine and compare the daily mortality rate of this organism in sputum and in physiological salt solution.

A five-day-old, yeast-phase culture of *H. capsulatum* was diluted serially in sputum and in physiological salt solution, and inocula from these dilutions were plated at once on several appropriate culture media. The diluted suspensions were kept at room temperature, and samples from each were plated daily. The numbers of viable organisms in the saline suspensions decreased gradually over a ten-day period as shown by the numbers of colonies recovered by daily platings. The suspensions of *H. capsulatum* in sputum, on the other hand, showed a sharp reduction in the number of viable cells after twenty-four hours. Samples removed and cultured after forty-eight hours yielded only a few colonies, and after three to four days no growth could be obtained. In a few instances the forty-eight-hour samples produced negative cultures. These findings occurred even when very large numbers of organisms were present in the sputum suspensions.

[1] From the Ray Brook State Tuberculosis Hospital, Ray Brook, New York.

Three possible causes for this adverse effect of sputum on *H. capsulatum* were considered: enzymes, bacteria present in the sputum, and variation in pH. To investigate these possibilities, autolysed sputum was passed through a Seitz filter and the bacteria-free filtrate was divided into two parts, one of which was heated to inactivate any enzymes present. Cells of *H. capsulatum* were suspended in each filtrate, and cultures were made daily as in the preceding experiment and, again, after three to four days the organisms could no longer be recovered.

In a preliminary survey of a large number of sputum specimens received both by mail and from house patients, a pH range of 6.0 to 8.0 was found, with the majority being acid in reaction. With this information in mind, yeast-phase cells of *H. capsulatum* were added to sputum samples having pH values of 6.0, 7.0, and 8.0. The suspensions were kept at room temperature and cultured daily. *H. capsulatum* could not be recovered after three to four days. On the basis of these tests, it appeared that the rapid death of this organism in sputum could not be attributed to any of these factors.

During the course of these studies a patient with nontuberculous pulmonary disease entered the hospital. *H. capsulatum* was recovered repeatedly from freshly expectorated sputum from this patient (2). When these specimens were kept at room temperature and cultured daily as described previously, the organism could not be recovered after three to four days (plate V, figures 1 and 4). Following this patient's discharge from the hospital, several sputum specimens were sent to this laboratory by mail, and in no instance could *H. capsulatum* be recovered. When the patient returned to the hospital for examination, growth was readily obtained from specimens sent to the laboratory soon after expectoration. These findings were obtained on several occasions. The organisms obtained from this patient's sputum were culturally and microscopically identical to the stock culture employed in the experimental studies under observation at that time.

This actual case experience lends support to the experimental observation and points to a distinct advantage in obtaining freshly expectorated sputum for the isolation of *H. capsulatum*.

IDENTIFICATION OF HISTOPLASMA CAPSULATUM

The identification of *H. capsulatum* is dependent upon certain cultural and morphologic characteristics which are best demonstrated by the simultaneous use of the following media: brain heart infusion blood agar (3) or modified Campbell's veal infusion blood agar (4) and Sabouraud's glucose agar. The first mentioned is prepared from Bacto brain heart infusion medium containing 2 per cent agar, and Bacto veal is used in the preparation of Campbell's medium. To each 100 ml. of either medium, 10 ml. of blood, 2,000 units of penicillin, and 4,000 γ of streptomycin are added (5). A generous loopful of purulent sputum is streaked heavily over the surface of the plates, which are then sealed with wide rubber bands to prevent drying of the medium. Two blood agar plates are incubated at 37°C. and two blood agar plates and two Sabouraud's plates at room temperature. The plates are examined twice weekly. *Monilia* colonies, which are frequently encountered, may be distinguished from *H. capsulatum* by their early appearance and development into large white colonies in forty-eight to seventy-two hours. All plates are discarded after four weeks of incubation.

The growth characteristics of *H. capsulatum* vary with the type of culture medium used and the incubation temperature On blood agar at 37°C., *H. capsulatum* colonies become visible after eight to twelve days. They are small, white or gray in color, and assume a light brown color with age. They may be smooth or slightly rough in appearance and resemble bacterial colonies. They are easily separated from the surface of the medium. A mycelial fringe may develop at the periphery of some of the colonies (plate II, figures 1, 2, and 3).

Microscopically, unstained slide preparations from these colonies show small, round, or oval budding cells, occurring singly or in pairs, in short chains and in small clusters. The oval cells are often sharply pointed at one pole and may contain one or more refractile fat droplets (6, 7) (plate II, figure 4).

When grown on blood agar at room temperature, *H. capsulatum* shows mycelial growth after fourteen to eighteen days. Two types of colonies may be found. One is flat and red-brown with a fine mycelial fringe which spreads over the surface a considerable distance from the dense, slightly raised central portion (plate III, figures 1 and 3). The second type is a small, round, elevated colony with a few aerial hyphae. When examined with a hand lens, spiny processes of varying size and number may be seen protruding from these colonies. A mycelial fringe is also present (plate III, figures 1, 2, and 4).

Microscopically, both types are similar. The majority are composed entirely of branching septate mycelia. Occasionally, thin, smooth-walled round or pyriform spores are seen, many of which contain one or more bodies resembling endospores (plate III, figure 5).

Tuberculate chlamydospores are not found on blood media, but these structures, so important in the identification of *H. capsulatum*, can be demonstrated by transplanting on Sabouraud's medium these yeastlike or mycelial colonies.

A white cottony type of growth is observed after fourteen to eighteen days at room temperature when sputum containing *H. capsulatum* is streaked on the surface of Sabouraud's glucose agar. The colonies develop abundant fine aerial hyphae and may turn light brown with age (plate IV, figures 1 and 2; plate V, figure 3).

Microscopically, these colonies are made up of masses of fine, branching, septate mycelia, along which thick-walled round or pyriform spores develop. These are variable in size and may contain numerous fat droplets which resemble endospores (6, 7). The walls are at first smooth, then highly refractile with a crenated outline; and, finally, the cells develop bulbous enlargements or spiny, finger-like projections surrounding the entire wall. These latter forms, tuberculate chlamydospores, are the distinguising morphologic characteristice of *H. capsulatum* (6, 7) (plate IV, figures 3 and 4).

DISCUSSION

The foregoing studies reveal the importance of obtaining freshly expectorated sputum specimens for the cultivation of *Histoplasma capsulatum*. It has been shown that, when sputum containing *H. capsulatum* is stored at room temperature, the fungus cannot be recovered after a relatively short time. The cause of this rapid death rate has not yet been determined.

The literature concerning the efficacy of various culture media in the cultivation of *H. capsulatum* contains observations which are confusing. The culture media are evaluated in several reports in which the experimentally infected organs of animals were used as the inocula, but there are no such reports on the isolation of *H. capsulatum* from sputum. Howell (3) compared the efficiency of brain heart infusion blood agar (BHI) and potato dextrose agar in culturing this organism from the spleen of infected guinea pigs. The highest percentage of positive cultures (80.4 per cent) was obtained on the BHI blood agar at room temperature, while incubation at 37°C. yielded only 13 per cent positive cultures. On potato dextrose agar, 41.3 per cent were positive at room temperature and none were positive at 37°C. The colonies from BHI blood agar at room temperature were atypical in appearance, being moist, heaped, and cerebriform. When these colonies were transferred to medium such as potato dextrose agar and incubated at room temperature, the characteristic tuberculate chlamydospores developed.

In a recent report on the isolation of *H. capsulatum* from the tissues of experimentally infected mice, Kotcher, Robinson, and Miller (8) obtained 95.2 per cent positive cultures on BHI blood agar and 97.6 per cent positives on Sabouraud's glucose agar when incubated at room temperature. These authors stated that the usefulness of BHI blood agar is limited because tuberculate chlamydospores do not develop on this medium.

The results in the present study, obtained from experimentally infected sputum and from the sputum of a patient with pulmonary histoplasmosis, show that either BHI blood agar or modified Campbell's blood agar are the most efficient media for the isolation of *H. capsulatum* from sputum. The same number of colonies was recovered on these media whether incubation was carried out at 37°C. or at room temperature although the character of the growth differed, being yeastlike at 37°C. and mycelial at room temperature (plate V, figures 1 and 2). Both of these colony types must be transferred to medium such as Sabouraud's and incubated at room temperature in order to obtain the characteristic tuberculate chlamydospores.

Sabouraud's glucose agar was found least suitable for the primary isolation of *H. capsulatum* from sputum. In the present experience, growth was obtained in only a few instances and then consisted of only one or two colonies, as compared with the large numbers obtained on the blood agar plates inoculated with the same material (plate V, figures 1 and 3). No growth was obtained on this medium when incubated at 37°C. The present results with this medium differ from those of Kotcher, Robinson, and Miller, but it is possible that the high percentage of positive cultures obtained by these workers from mouse splenic tissue might be due to the added nutriment of tissue juice or blood carried over to the surface of the medium.

The difficulty in isolating *H. capsulatum* from sputum can be almost entirely eliminated by using freshly expectorated material in which few contaminating organisms are present. The addition of penicillin and streptomycin to media, as recommended by Thompson (5), has been of great value. *Monilia*, frequently encountered in the bacteriologic examination of sputum, can be readily distinguished from *H. capsulatum* by its more rapid growth.

SUMMARY

It has been shown that *Histoplasma capsulatum* dies rapidly in sputum. It is therefore recommended that freshly expectorated material be cultured in attempts to isolate this organism.

The method of cultivation on suitable media and the cultural and morphologic characteristics are described, and detailed illustrations are given to aid in the identification of *H. capsulatum*.

SUMARIO

Aislamiento del Histoplasma Capsulatum del Esputo

Está demostrado que el *Histoplasma capsulatum* muere rápidamente en el esputo, por lo cual se recomienda el cultivo de material recién expectorado con mira a aislar el microbio.

Descríbense la técnica de cultivo en medios apropiados y las características culturales y morfológicas, a la par que se ofrecen grabados pormenorizados que ayuden en la identificación del *H. capsulatum*.

RESUME

Isolement de l'Histoplasma capsulatum à partir de crachats

L'auteur montre que *l'Histoplasma capsulatum* meurt rapidement dans les crachats. En conséquence, il est recommandé d'utiliser pour les culture des expectorations fraîches si on veut isoler ce microorganisme.

La technique de sa culture sur un milieu adéquat est décrite ainsi que sa morphologie. Des illustrations détaillées facilitent l'identification de *H. capsulatum*.

Acknowledgment

I am indebted to Dr. Diran Yegian for the many helpful suggestions during the course of the investigation.

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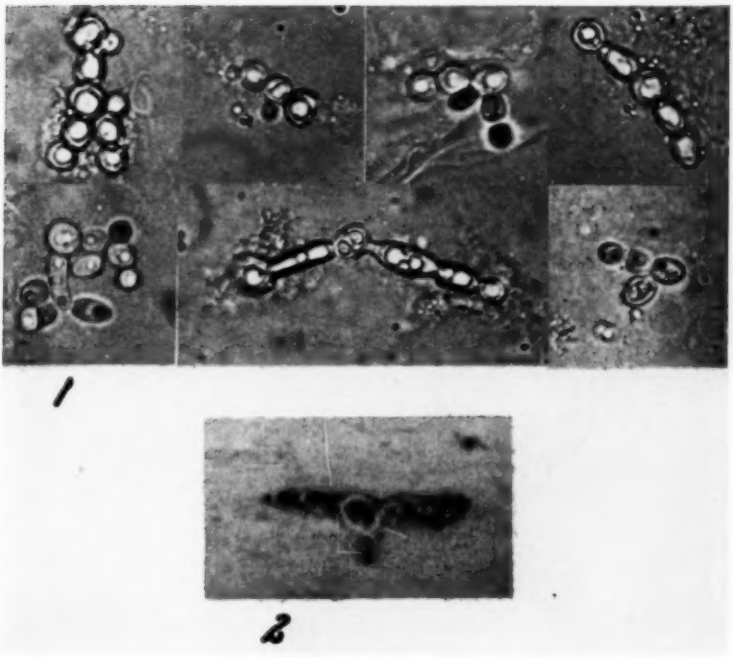

Plate I

FIG. 1. Sodium hydroxide preparation of freshly expectorated sputum, obtained directly from a patient with pulmonary histoplasmosis, showing several different variations of *H. capsulatum* cells.

FIG. 2. Wright's stain made from the same specimen of sputum, showing the close resemblance of these organisms to those found in stained pathologic material.

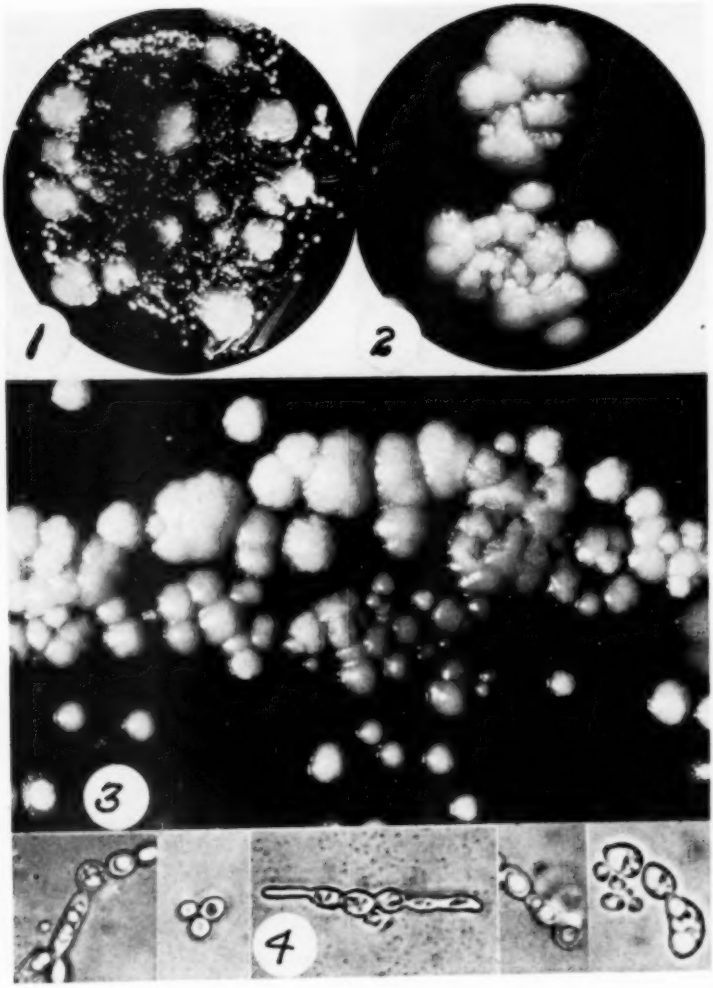

Plate II

FIG. 1. Actual size photograph of a blood agar plate streaked with sputum from a patient with pulmonary histoplasmosis, incubated at 37°C. for three weeks, showing numerous small yeast-phase colonies of *H. capsulatum*. The few large colonies are *Monilia*.

FIG. 2. Slightly magnified view of the small cluster of colonies seen near the border and just above the right center shown in figure 1. (×10)

FIG. 3. Another slightly magnified view of the colonies along the line of streak seen at the top of figure 1. Note the presence of a mycelial fringe around a few of the colonies. (×10)

FIG. 4. Unstained slide preparation made from the small colonies seen in figure 1, showing the yeastlike budding cells of *H. capsulatum* in various forms. (×1,000)

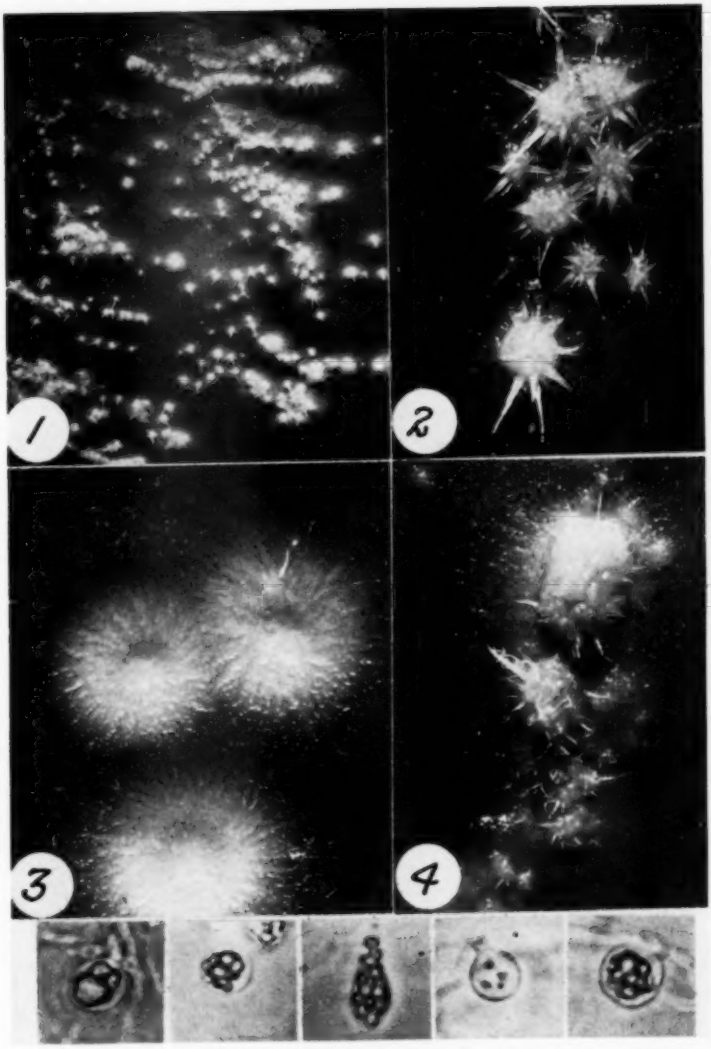

Plate III

FIG. 1. Actual-size photograph of a blood agar plate streaked with sputum from the same patient with histoplasmosis and incubated at room temperature for three weeks. The colonies are mycelial in character, many with aerial hyphae.

FIGS. 2 and 4. Slightly magnified views of the colonies with aerial hyphae shown in figure 1. (×10)

FIG. 3. Slightly magnified view of the flat spreading type of colony. (×10)

FIG. 5. (Bottom) Unstained slide preparation made from colonies grown on blood agar at room temperature, showing the smooth-walled round or pyriform spores. (×1,000)

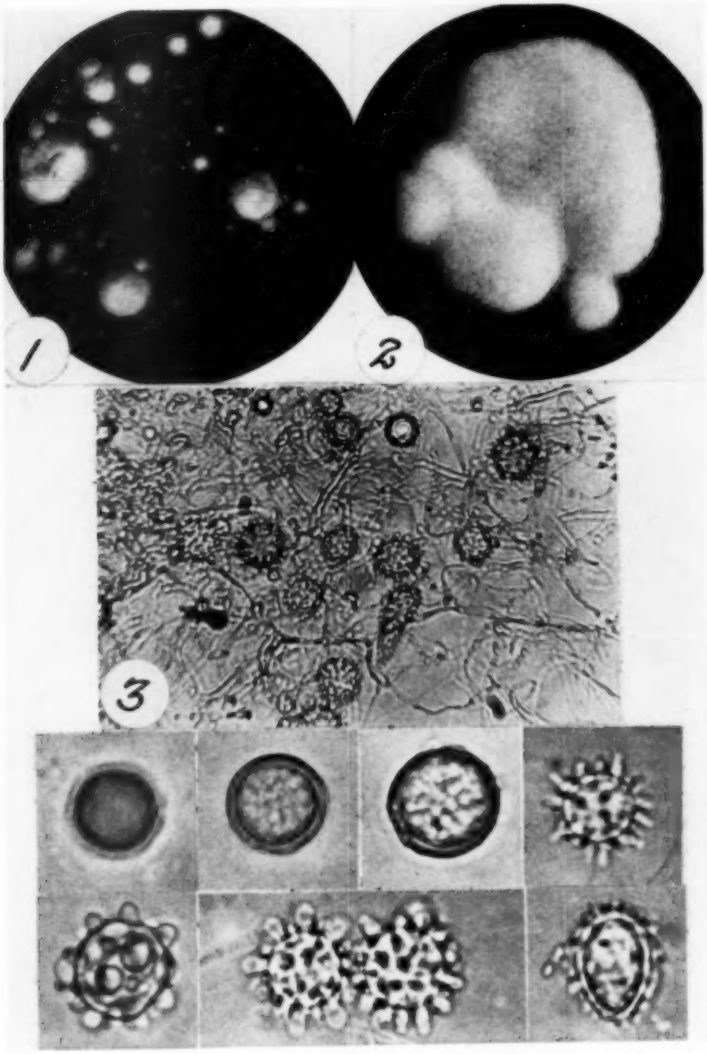

Plate IV

FIG. 1. Actual-size photograph of a cottony growth of *H. capsulatum* on Sabouraud's glucose agar after three weeks of incubation at room temperature.

FIG. 2. Slightly magnified view of a cottony or mycelial colony. (×5)

FIG. 3. Unstained slide preparation, showing mycelia and tuberculate chlamydospores. (×400)

FIG. 4. (Bottom) Highly magnified views of chlamydospores, showing various stages of development from the round smooth-walled spores to the characteristic tuberculate chlamydospores. (×1,000)

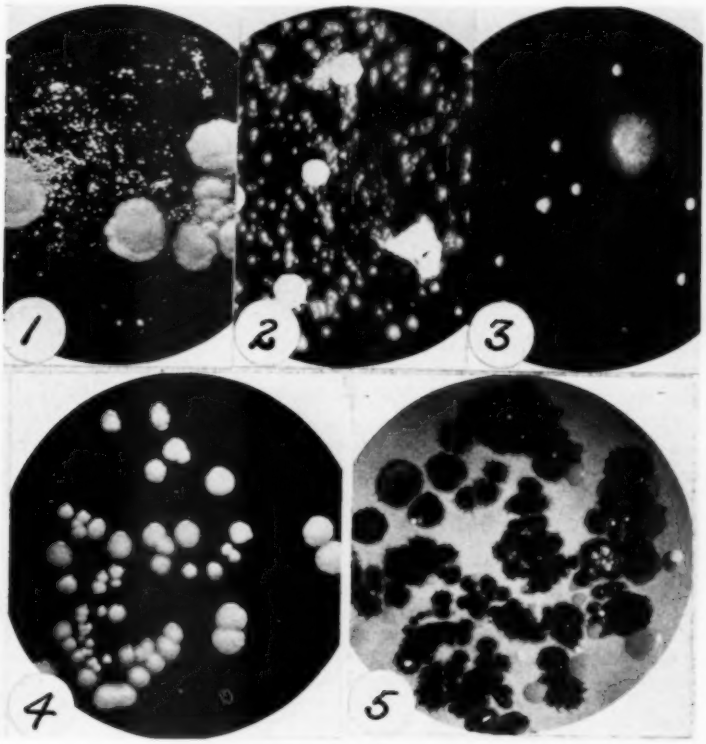

Plate V

Actual-size comparison photographs of cultures of the sputum from a patient with pulmonary histoplasmosis.

FIG. 1. Blood agar plate of freshly expectorated sputum, incubated at 37°C., showing large numbers of *H. capsulatum* colonies and a few *Monilia* colonies.

FIG. 2. Blood agar plate, inoculated as above but incubated at room temperature, showing mycelial growth. Aerial hyphae can be seen on some colonies.

FIG. 3. Sabouraud's glucose agar inoculated at the same time, showing a single colony of *H. capsulatum*.

FIG. 4. Blood agar plate, inoculated with the same sputum specimen which had been kept at room temperature for four days, showing complete absence of *H. capsulatum* colonies regardless of incubation temperature. The colonies seen are *Monilia*.

FIG. 5. Culture of mailed-in sputum specimen from the same patient, showing the many contaminating molds, yeasts, and bacteria which may be encountered in this type of specimen.

EFFECT OF REPEATED HISTOPLASMIN SKIN TESTS ON SKIN REACTIVITY AND COLLODION AGGLUTINATION[1,2]

JOHN A. PRIOR AND SAMUEL SASLAW

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INTRODUCTION

With the growing interest in histoplasmosis, there has been a concomitant increase in the use of the histoplasmin skin test as a diagnostic aid. To evaluate this procedure more fully, it is necessary to know whether repeated histoplasmin skin tests can enhance or depress the skin reactivity or even possibly result in conversion or reversion. In addition, the question arises in the study of histoplasmosis, as it has in other diseases, whether repeated intradermal injections of antigen can alter the humoral antibody titer.

Although it has been shown that a single histoplasmin skin test does not affect serologic titers (1), controlled studies in man to determine the effect of repeated injections on both skin reactivity and antibody formation are lacking. Therefore, the following investigation was undertaken to ascertain the influence of repeated intradermal injections of histoplasmin upon: (*a*) the skin reactivity and (*b*) the serologic reaction. The collodion agglutination test was used for the latter study (2, 3).

METHOD

Twenty-two healthy medical students, most of whom were life-long residents of Ohio, were selected at random for this study. Immediately after drawing blood for base-line serologic studies, an intradermal skin test was performed, using 0.1 cc. of a 1:100 dilution of histoplasmin (H-40).[3] Fresh dilutions of histoplasmin were prepared each week. At weekly intervals for seven succeeding weeks, the subjects were bled and then given repeat skin tests. After each injection, the skin test was read forty-eight hours later, the induration recorded in millimeters; 5.0 mm. or more of induration was considered to be "positive." Seven months after this test period, another sample of blood was obtained for comparison whenever possible.

As a control, a similar group of volunteers was subjected to a single histoplasmin skin test after blood had been obtained for base-line serologic studies. Blood was drawn at weekly intervals for four weeks after injection.

All sera from both groups were tested by means of the collodion agglutination reaction for histoplasmosis.

RESULTS

Fifteen of 22 students in the group which received repeated skin tests showed a definite reaction on the initial reading (table 1). Following repeated intradermal injections, some variation in the transverse diameter of the induration was observed. It should be noted that on the third week after the initial test several

[1] From the Department of Medicine, Ohio State University, Columbus, Ohio.

[2] This project was aided by a grant from the Ohio Tuberculosis and Health Association, in cooperation with the Medical Research Committee of the American Trudeau Society, medical section of the National Tuberculosis Association.

[3] Kindly furnished by Dr. Arden Howell, Jr., mycologist, Public Health Service.

TABLE 1

SKIN SENSITIVITY AND COLLODION AGGLUTINATION FOLLOWING REPEATED INTRADERMAL INJECTIONS OF HISTOPLASMIN

SUBJECT NUMBER	WEEKS AFTER FIRST SKIN TEST								
	0	1	2	3	4	5	6	7	35
1 S. T.*	15	15	8	25	15	15	15		
C. A.†	0	0	0	0	0	0	0	0	
2	7	7	7	7	7	7	7		
	0	0	0	0	0	0	0	0	
3	22	12	15	50	10	15	15		
	0	0	0	0	0	0	1:10	0	0
4	12	6	8	25	20	15	20		
	0	0	0	0	0	0	0	0	
5	N	N	N	N	N	N	N		
	0	0	0	0	0	0	0	0	
6	N	N	N	N	N	N	N		
	0	0	0	0	0	0	0	0	
7	8	14	12	15	14	14	14		
	0	0	0	1:10‡	1:5‡	0	0	0	0
8	5	10	25	12	20	10	10		
	0	0	0	1:80	1:80	1:20	1:20	0	0
9	N	N	N	N	N	N	N		
	0	0	0	0	0	0	0	0	0
10	12	12	12	25	20	10	9		
	0	0	1:40	1:80	1:320	1:20	1:80	1:40	0
11	N	N	N	N	N	N	N		
	0	0	0	0	0	0	0	0	0
12	N	N	N	N	N	N	N		
	0	0	0	0	0	0	0	0	0
13	5	6	12	10	8	8	10		
	0	0	0	0	0	0	1:5‡	0	0
14	2	7	8	10	N	N	N		
	0	0	0	0	0	0	0	0	0
15	10	24	15	25	20	16	8		
	0	0	0	1:5‡	0	0	0	0	0
16	10	12	15	15	8	10	20		
	0	0	0	1:20	1:10	0	0	0	
17	N	N	N	N	N	N	N		
	0	0	0	0	0	0	0	0	0
18	10	35	10	15	18	15	15		
	0	0	0	0	0	0	1:10‡	0	0
19	20	15	20	46	10	10	10		
	0	0	0	0	0	0	0	0	
20	15	10	17	10	17	15	15		
	0	0	0	0	0	0	1:10	0	0
21	15	15	15	15	12	12	12		
	0	0	0	0	0	0	0	0	
22	10	10	20	32	10	10	10		
	0	0	0	0	1:20	1:10	1:20	1:5‡	0

* Skin test reactions are recorded in millimeters of induration. N—designates no skin reaction.

† Number opposite collodion agglutination tests indicates the highest titer showing three or four plus agglutination.

‡ Three-plus agglutination only.

subjects showed a considerable increase in the skin reaction. Since this did not persist, it is believed that this alteration, as well as the other less marked changes, was the result of biologic and technical variation. Thus, no significant change in the skin reactivity was noted in the histoplasmin-positive group as the result of the repeated injections.

Of the 7 students who did not react to histoplasmin, none developed skin sensitivity as the result of the repeated injections. One possible exception was subject *14*, who exhibited a positive skin test for a brief period and then failed to react to the final three tests. It should be noted that after the initial skin test there was slight induration (2.0 mm.) but not sufficient to be considered positive.

None of the sera from the group which received repeated histoplasmin injections reacted in the collodion agglutination test prior to the administration of the first skin test. In the histoplasmin-negative group, none showed any antibody response following the repeated histoplasmin injections. Nevertheless, of the 15 skin-test-positive students, 10 showed some alteration in humoral antibody titer. The most marked reactions were found in subjects *8* and *10*, whose sera began to show strong agglutination titers after the third and second weeks, respectively; peak levels of 1:80 and 1:320 were observed after three and four weeks. In subject *8*, the titer was transient and had returned to insignificant levels by the seventh week. In subject *10*, however, the titer had decreased but still was positive in a dilution of 1:40 at the end of the seventh week. A specimen obtained from this person after thirty-five weeks showed no reaction in the serologic test. To a lesser degree, sera from subjects *16* and *22* showed titers of 1:20 in the third and fourth weeks but were negative by the fifth and seventh weeks, respectively. The sera of 2 persons (subjects *3* and *20*) showed a transient increase in agglutinating capacity at dilutions of 1:10 during the seventh week only. Four subjects (subjects *7*, *13*, *15*, and *18*) showed three-plus reactions in dilutions of 1:5 or 1:10 on only one occasion between the third and seventh weeks except for subject *7*, whose serum reacted over a two-week period.

For comparative purposes, serial blood specimens obtained from 12 volunteers following a single intradermal injection were studied. Of this group, 5 were skin-test-positive and 7 were negative. In none of these persons was there any detectable increase in antibody titer over a subsequent four-week period. This is in agreement with previous observations that a single skin test does not affect the histoplasma antibody titer (1).

DISCUSSION

Usually the patient with the protean manifestations of histoplasmosis presents a difficult diagnostic problem and, when seen by the internist, has often been sick for weeks or even months. A definite diagnosis frequently requires diligent study. As a consequence, many diagnostic procedures may be performed. In some instances, the histoplasmin skin test may have been applied several times. To fully evaluate this procedure, it is essential to know what effect the repeated intradermal injections of histoplasmin may have on the skin reactivity and serologic reaction.

Tukey, DuFour, and Seibert (5) have demonstrated that repeated skin tests with tuberculin do not alter significantly the skin reactivity. Howell (6) has shown that repeated intradermal injections of 1:100 dilutions of various lots of histoplasmin and blastomycin did not sensitize normal guinea pigs. In a similar manner, it has been shown in the present study that there is no significant alteration in the skin reaction following seven weekly intradermal injections of histoplasmin.

Cultural proof of the presence of *H. capsulatum* is most desirable for a diagnosis of histoplasmosis. Often this cannot be obtained, and thus indirect methods, e.g., serologic tests, have proved to be of considerable value in confirming the clinical impression or in initiating the search for the causative fungus (7, 8).

Although a single skin test has been shown to have no effect on the serologic results (1), the response to repeated injections has not been adequately studied. Four-plus collodion agglutinations in serum dilutions greater than 1:5 have not ordinarily been observed in "normal" individuals, and collodion agglutination titers of 1:20 or more were associated with active histoplasmosis (7). Four-plus reactions at 1:10 have been considered suspicious and suggest a diligent search for *H. capsulatum*. Repeated histoplasmin skin tests conceivably could alter the serologic picture and result in "false positives." Therefore, serial serum specimens were obtained for comparison following weekly repeated skin tests. It is of interest to note that alterations in serum titer were noted only in the skin-test–positive group; 10 of 15 reactors showed an increase in humoral antibodies. This would suggest that, in the skin-test–positive group, antibodies were present but not detected in the serum by the collodion agglutination test and that, as a result of repeated histoplasmin tests, a booster effect was obtained.

Thus, in the present preliminary study, the sera of 6 subjects showed transient titers sufficiently high to be considered suggestive of active disease; four-plus agglutinations from 1:10 to 1:320 were observed. All sera were negative at the end of the seventh week except subject *10's*, whose serum showed no reaction when checked thirty-five weeks after the first skin test. Four volunteers showed increased reactivity (three-plus agglutination at 1:5 or 1:10) on only one occasion between the fourth and seventh weeks except subject *7*, whose serum reacted in the fourth and fifth weeks. Thus, using the same antigen in a serologic test (collodion agglutination) as is used in skin testing, false positive serologic reactions were observed following repeated intradermal injections. Whether this would occur in the complement-fixation test, using yeast phase or histoplasmin antigens, is not yet definitely known. Studies on this particular aspect are now in progress in this laboratory. No change was noted in the skin-test–negative group which received repeated injections or in the control group of 5 positive reactors and 7 nonreactors following a single injection.

SUMMARY

No significant change in skin reactivity was noted in 22 healthy volunteers following weekly histoplasmin skin tests for seven weeks.

Ten of 15 histoplasmin skin reactors showed alteration in humoral antibody titers. Transient collodion agglutinations which might be considered significant

appeared in the serum of 6 histoplasmin reactors between the third and sixth weeks after the initial skin test. Of the remaining skin reactors, 4 showed slight transient reactions. Thus, repeated weekly histoplasmin skin tests may result in "false positive" collodion agglutination reactions in skin-test–positive individuals. None of the skin-test-negative group showed any antibody response.

Of the control group which received only a single skin test, no alteration in humoral antibodies was noted during the subsequent four-week period.

SUMARIO

Efecto de las Cutirreacciones Repetidas con Histoplasmina sobre la Cutirreactividad y la Aglutinación del Colodión

No se notó mayor alteración de la reactividad cutánea consecutivamente a cutirreacciones semanales con histoplasmina durante siete semanas en 22 voluntarios sanos.

Diez de 15 cutirreactores mostraron alteración de los títulos de anticuerpos humorales. En el suero de 6 reactores a la histoplasmina aparecieron entre la tercera y la sexta semanas subsiguientes a la cutirreacción inicial aglutinaciones pasajeras del colodión que podrían considerarse como significativas. De los cutirreactores restantes, 4 revelaron leves reacciones pasajeras. Las repetidas cutirreacciones semanales con histoplasmina pueden, pues, dar por resultado aglutinorreacciones "seudopositivas" con colodión en los cutirreactores. Ninguno de los cuti-negativos mostró la menor respuesta en anticuerpos.

En el grupo testigo en que se ejecutó una sola cutirreacción, no se notó ninguna alteración de los anticuerpos humorales durante el subsiguiente período de cuatro semanas.

RESUME

Effet des tests cutanés à l'histoplasmine répétés sur la réactivité cutanée et l'agglutination au collodion

Aucune modification appréciable de la réactivité cutanée n'a été notée à la suite d'une série de tests à l'histoplasmine, répétés chaque semaine pendant sept semaines, chez 22 volontaires bien portants.

Parmi les 15 présentant une réaction cutanée, 10 sujets ont présenté des modifications du titre humoral en anticorps. Après le test cutané initial, des réactions transitoires d'agglutination au collodion, pouvant être considérées comme significatives, sont apparues entre la troisième et la sixième semaine dans le sérum de 6 sujets réagissant à l'histoplasmine. Dans le reste du groupe présentant une réaction cutanée, 4 ont présenté des réactions modérées transitoires. Donc les tests cutanés hebdomadaires répétés peuvent déterminer des résultats "faussement positifs" des réactions d'agglutination au collodion chez les individus ayant un test cutané positif. Aucun des sujets du groupe à cuti-réaction négative n'a montré la réaction anticorps.

Dans le groupe-témoin soumis à un seul test cutané, il n'a été observé aucune modification du titre humoral des anticorps pendant les quatre semaines suivantes.

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A COMPARATIVE EVALUATION OF THE HEMAGGLUTINATION TEST AND THE HEMOLYTIC MODIFICATION IN TUBERCULOSIS[1,2]

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INTRODUCTION

There have been many attempts in the past to develop a serologic method for determining the activity of a tuberculous process (1). All of these tests were discarded in the course of time, however, because of their lack of specificity. In 1948, Middlebrook and Dubos (2) described a hemagglutination test which could detect specific antibodies in the sera of tuberculous animals and humans. In this test they employed a new type of antigen consisting of sheep erythrocytes sensitized by adsorption of the water-soluble extract of human tubercle bacilli. Scott and Smith (3) modified this hemagglutination test by substituting Old Tuberculin four times the standard strength (Lederle) for an aqueous extract of human tubercle bacilli as the sensitizing agent for the sheep erythrocytes. In 1950, Middlebrook (4) described a hemolytic modification of the hemagglutination test, which consisted of the addition of a constant amount of fresh, "absorbed complement" to each tube of the hemagglutination reaction system. His observations indicated that sheep erythrocytes sensitized by adsorption of concentrated tuberculin can be hemolyzed by addition of "absorbed complement" and serum containing specific antibodies.

The present investigation was made in order to ascertain the comparative clinical value of the hemagglutination test and its hemolytic modification.

MATERIAL AND METHODS

During the sixteen-month period, May, 1950 to September, 1951, the hemagglutination test and the Middlebrook hemolytic modification of this test were performed on the following groups of subjects:

A group of 71 patients with active pulmonary tuberculosis: All of these patients had roentgenographic evidence of unstable pulmonary lesions as well as sputum positive for acid-fast bacilli.

A group of 200 patients with inactive pulmonary tuberculosis: All of these patients were ambulatory and asymptomatic with repeatedly negative sputum and gastric cultures for *M. tuberculosis* during the preceding year or longer. Serial chest roentgenograms had revealed that the lesions had been stable for a minimum period of one year.

A group of 50 patients with various forms of chronic nontuberculous pulmonary diseases.

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[1] From the Veterans Administration Regional Office, Brooklyn, New York.

[2] Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

A control group of 297 normal adults: This series consisted of persons who had been found free from pulmonary or other systemic diseases. Tuberculin tests were not performed.

The hemagglutination test and its hemolytic modification were carried out on the sera of all of the 678 subjects according to the procedure described by Middlebrook (4). The details of the technique are contained in Middlebrook's

TABLE 1

RESULTS OF HEMAGGLUTINATION AND HEMOLYTIC TESTS PERFORMED ON THE SERA OF 297 NORMAL ADULTS

TEST	NO REACTION IN ANY TUBE	TUBE NO. 1 TITER 1:4	TUBE NO. 2 TITER 1:8	TUBE NO. 3 TITER 1:16	TUBE NO. 4 TITER 1:32	TUBE NO. 5 TITER 1:64	TUBE NO. 6 TITER 1:128	TUBE NO. 7 TITER 1:256
Hemagglutination test	71 (23.9%)	78 (26.3%)	78 (26.3%)	49 (16.5%)	16 (5.4%)	5 (1.6%)	0 (0%)	0 (0%)
Hemolytic test	255 (85.9%)	3 (1.0%)	12 (4.0%)	4 (1.4%)	12 (4.0%)	10 (3.4%)	1 (0.3%)	0 (0%)

TABLE 2

RESULTS OF HEMAGGLUTINATION AND HEMOLYTIC TESTS PERFORMED ON THE SERA OF 260 PATIENTS WITH INACTIVE PULMONARY TUBERCULOSIS

TEST	INACTIVE PULMONARY TUBERCULOSIS	NO REACTION IN ANY TUBE	TUBE NO. 1 TITER 1:4	TUBE NO. 2 TITER 1:8	TUBE NO. 3 TITER 1:16	TUBE NO. 4 TITER 1:32	TUBE NO. 5 TITER 1:64	TUBE NO. 6 TITER 1:128	TUBE NO. 7 TITER 1:256
Hemagglutination test	Minimal	35	21	32	18	7	2	2	0
	Moderately advanced	36	18	26	20	13	6	2	0
	Far advanced	4	7	4	4	5	0	0	0
	Totals	75 (28.8%)	46 (17.7%)	62 (23.8%)	40 (15.4%)	25 (9.6%)	8 (3.1%)	4 (1.6%)	0 (0%)
Hemolytic test	Minimal	87	4	9	7	3	3	0	2
	Moderately advanced	75	6	8	12	11	4	2	3
	Far advanced	16	3	0	2	0	1	2	0
	Totals	178 (68.5%)	13 (5.0%)	17 (6.5%)	21 (8.1%)	14 (5.4%)	8 (3.1%)	4 (1.6%)	5 (1.8%)

report and, therefore, need not be repeated here.[3] The titers of the hemagglutination and hemolytic reactions have been expressed in terms of the final dilution of the serum after addition of the antigen. Therefore, tube No. 1 represents a 1:4 dilution; tube No. 2, a 1:8 dilution; tube No. 3, a 1:16 dilution, et cetera.

RESULTS

The results obtained with the hemagglutination and hemolytic tests in the various groups are shown in tables 1, 2, 3, and 4. The percentage of technical

[3] The Old Tuberculin 4× standard strength employed in these tests was generously supplied by Lederle Laboratories, Pearl River, New York.

TABLE 3

Results of Hemagglutination and Hemolytic Tests Performed on the Sera of 71 Patients with Active Pulmonary Tuberculosis

TEST	ACTIVE PULMONARY TUBERCULOSIS	NO REACTION IN ANY TUBE	TUBE NO. 1 TITER 1:4	TUBE NO. 2 TITER 1:8	TUBE NO. 3 TITER 1:16	TUBE NO. 4 TITER 1:32	TUBE NO. 5 TITER 1:64	TUBE NO. 6 TITER 1:128	TUBE NO. 7 TITER 1:256
Hemagglutination test	Minimal	0	0	5	1	4	1	1	2
	Moderately advanced	1	3	10	5	5	6	3	1
	Far advanced	2	2	3	6	5	2	0	3
	Totals	3 (4.2%)	5 (7.1%)	18 (25.3%)	12 (16.9%)	14 (19.7%)	9 (12.7%)	4 (5.6%)	6 (8.5%)
Hemolytic test	Minimal	1	1	0	2	2	1	2	2
	Moderately advanced	5	2	3	9	4	3	3	5
	Far advanced	7	1	2	0	2	4	2	5
	Totals	13 (18.3%)	4 (5.6%)	5 (7.1%)	11 (15.5%)	8 (11.2%)	11 (15.5%)	7 (9.9%)	12 (16.9%)

TABLE 4

Results of Hemagglutination and Hemolytic Tests Performed on the Sera of 50 Patients with Nontuberculous Pulmonary Diseases

TEST	NO REACTION IN ANY TUBE	TUBE NO. 1 TITER 1:4	TUBE NO. 2 TITER 1:8	TUBE NO. 3 TITER 1:16	TUBE NO. 4 TITER 1:32	TUBE NO. 5 TITER 1:64	TUBE NO. 6 TITER 1:128	TUBE NO. 7 TITER 1:256
Hemagglutination test	30 (60%)	7 (14%)	7 (14%)	4 (8%)	2 (4%)	0 (0%)	0 (0%)	0 (0%)
Hemolytic test	44 (88%)	0 (0%)	4 (8%)	0 (0%)	2 (4%)	0 (0%)	0 (0%)	0 (0%)

TABLE 5A

Variation in the Titers of Two Hemagglutination Tests Repeated in 84 Subjects

TITER DIFFERENCE	TOTAL NUMBER (84)	ACTIVE TUBERCULOSIS (11)	INACTIVE TUBERCULOSIS (56)	NONTUBERCULOUS (17)
None	35 (41.7%)	2 (18.2%)	22 (39.4%)	11 (64.8%)
1 tube	33 (39.3%)	6 (54.5%)	24 (42.8%)	3 (17.6%)
2 tubes	16 (19.0%)	3 (27.3%)	10 (17.8%)	3 (17.6%)
More than 2 tubes	0	0	0	0

error in these procedures is relatively small, as is indicated by the consistent results obtained on repeating these tests on the serum of the same person at intervals varying from ten days to four months, while the clinical status remained unchanged. This is shown in tables 5A and 5B.

TABLE 5B

VARIATION IN THE TITERS OF TWO HEMOLYTIC TESTS REPEATED IN 84 SUBJECTS

TITER DIFFERENCE	TOTAL NUMBER (84)	ACTIVE TUBERCULOSIS (11)	INACTIVE TUBERCULOSIS (56)	NONTUBERCULOUS (17)
None	62 (73.8%)	6 (54.5%)	43 (76.8%)	13 (76.5%)
1 tube	10 (11.9%)	3 (27.3%)	6 (10.7%)	1 (5.9%)
2 tubes	12 (14.3%)	2 (18.2%)	7 (12.5%)	3 (17.6%)
More than 2 tubes	0	0	0	0

DISCUSSION

With the hemagglutination test, only 23.9 per cent of the sera from normal persons and 28.8 per cent of the sera from patients with inactive tuberculosis yielded completely negative results in all tubes. Therefore, if the hemagglutination test is to be of any significance in detecting active tuberculous disease, it must be evaluated quantitatively since specific antibodies in low titers may be present in the sera of persons with healed tuberculous foci of either primary or reinfection type. In addition, some of these mild reactions may be due to nonspecific factors not as yet ascertained. Nevertheless, a positive reaction in the higher titers represents a high specific antibody content of the serum which may be attributable to active infection with tubercle bacilli. For these reasons, the hemagglutination reactions have been classified into two categories: (*1*) nonsignificant reactions and (*2*) significant reactions. Analyzing the results obtained with this test in the normal subjects and in the group with inactive pulmonary tuberculosis, it was found that the optimum titer which could appropriately serve as the demarcation between "significant" and "nonsignificant" reactions was at tube No. 3. Therefore, all positive hemagglutination reactions appearing in any of the first three tubes, as well as entirely negative reactions in all tubes, have been grouped under the heading of "nonsignificant reactions." The term "significant reactions" has been applied to positive reactions occurring in tube No. 4 or higher. (The division between these two classes of reactions is indicated in tables 1, 2, 3, and 4 by double lines.) Based on these criteria, it was found that the hemagglutination tests yielded a "nonsignificant reaction" in 93.0 per cent of normal adults and in 85.7 per cent of a group with inactive pulmonary tuberculosis. Applying this classification to the group with active tuberculosis, it is noted that only 46.5 per cent yielded "significant reactions."

With the hemolytic test, on the other hand, 85.9 per cent of the sera from control subjects and 68.5 per cent of the sera from persons with inactive tuberculosis yielded negative results in all tubes. In this respect, the hemolytic test was superior to the hemagglutination test. However, any positive hemolytic reaction cannot be considered a reliable indicator of active tuberculosis, since positive reactions were also obtained in 31.5 per cent of the inactive cases. Therefore, in order that the hemolytic test may be useful clinically in determining the existence of an active tuberculous infection, it is necessary to classify the reactions as either "significant" or "nonsignificant," according to the same criteria employed in the evaluation of the hemagglutination test. When the hemolytic titers were interpreted in this manner, it was found that only 53.5 per cent of the active cases had "significant reactions." A "nonsignificant reaction," therefore, will not exclude the presence of active tuberculosis. However,

TABLE 6

COMPARISON OF HEMAGGLUTINATION AND HEMOLYTIC ANTIBODY TITERS IN THE SAME INDIVIDUALS

TITER DIFFERENCE	NORMAL SUBJECTS (297)	ACTIVE PULMONARY TUBERCULOSIS (71)	INACTIVE PULMONARY TUBERCULOSIS (260)	NONTUBERCULOUS PULMONARY DISEASES (30)
None	86	11	82	28
1 tube	77	18	69	5
2 tubes	69	18	49	10
3 tubes	49	13	33	6
4 tubes	12	3	15	1
5 tubes	4	4	8	0
6 tubes	0	1	4	0
7 tubes	0	3	0	0

a "significant reaction" will be a good indication of such activity, since only 11.9 per cent of the sera from inactive cases and 7.7 per cent of the sera from the control subjects were found to yield similar reactions.

When both the hemagglutination and hemolytic reactions are interpreted in this way, the over-all results obtained with these two tests become comparable. However, the titers obtained with these tests are not necessarily similar in each individual case. This is in accord with the observations of Middlebrook (4), who believes that these tests measure different types of specific antibodies produced in response to infection with tubercle bacilli. The results obtained with these tests in the same subjects are shown in table 6. The results obtained with the hemagglutination and the hemolytic tests have been further analyzed in order to determine whether a combination of the findings had any special significance. It was found that, on the whole, a combination of the readings of the two tests offers no advantage over the results obtained with the hemolytic method alone.

SUMMARY

An evaluation of the clinical significance of the hemagglutination test and its hemolytic modification was made on a series of 678 persons, composed of

297 normal adults, 260 persons with inactive pulmonary tuberculosis, 71 with active pulmonary tuberculosis, and 50 with various forms of nontuberculous pulmonary diseases.

In order that the hemagglutination and hemolytic tests may be useful clinically in the determination of tuberculous activity, it has been found expedient to classify the reactions into two groups: (*1*) nonsignificant reactions, which consist of all completely negative reactions as well as all positive reactions occurring in any of the first three tubes (dilutions 1:4, 1:8, and 1:16); (*2*) significant reactions, which comprise all positive reactions occurring in tube No. 4 or above (dilution 1:32 or above).

A "nonsignificant reaction" with either test does not exclude active tuberculosis, since approximately 50 per cent of the active cases have been noted to produce such reactions. However, if a "significant reaction" is obtained with either test, the likelihood that active tuberculosis exists is very great, since only approximately 7 per cent of normal persons and approximately 12 to 14 per cent of those with inactive pulmonary tuberculosis have been found to yield such serologic reactions with both the hemolytic and hemagglutination methods.

When the reactions are interpreted in this manner, the over-all results with these two methods are comparable. However, the reactions obtained with these tests in any one person are not necessarily similar.

There is no additional diagnostic aid derived from performing both tests in place of the hemolytic test alone.

SUMARIO

Justipreciación Comparada de la Hemaglutinorreacción y de la Modificación Hemolítica de la Misma en la Tuberculosis

En una serie de 678 personas, compuesta de 297 adultos normales, 260 con tuberculosis pulmonar inactiva, 71 con tuberculosis pulmonar activa y 50 con varias formas de afecciones pulmonares no tuberculosas.

A fin de que las pruebas de la hemaglutinación y hemolítica resulten útiles clínicamente en la determinación de la actividad tuberculosa, resultó conveniente clasificar las reacciones en dos grupos: (1) reacciones sin significación, que comprenden todas las absolutamente negativas así como todas las positivas observadas en los primeros tres tubos (diluciones al 1:4, 1:8 y 1:16); (2) reacciones significativas, que abarcan todas las positivas observadas en el tubo No. 4 ó los siguientes para arriba (dilución al 1:32 ó más).

Con una u otra prueba, una "reacción sin significación" no excluye la tuberculosis activa, pues se ha notado que aproximadamente 50 por ciento de los casos activos producen tales reacciones. Sin embargo, si se obtiene una "reacción significativa" con una u otra prueba, es muy grande la probabilidad de que exista tuberculosis activa, pues sólo aproximadamente 7 por ciento de las personas normales y no más de unos 12 a 14 por ciento de las que tienen tuberculosis pulmonar inactiva acusaron tales serorreacciones con ambas técnicas: la hemolítica y la de hemaglutinación.

Interpretadas las reacciones en esa forma, son comparables los resultados globales obtenidos con los dos métodos. Sin embargo, no son forzosamente semejantes las reacciones conseguidas con esas pruebas en una persona dada.

El diagnóstico no deriva ninguna ventaja más de la ejecución de ambas pruebas que de la henolítica sola.

RESUME

Une évaluation comparative du test d'hémagglutination et la modification hémolytique en tuberculose

Une évaluation de la valeur clinique du test d'hémagglutination et de sa modification hémolytique a été établie d'après une série de 678 individus composée de 297 adultes normaux; 260 sujets présentant une tuberculose pulmonaire stabilisée, 71 avec une tuberculose pulmonaire en activité et 50 atteints de diverses affections pulmonaires non tuberculeuses.

De manière à ce que les tests d'hémagglutination et d'hémolyse puissent avoir une valeur clinique pour la détermination de l'activité tuberculeuse, il a été trouvé utile de classer les réactions en deux groupes: (1) réactions non significatives englobant toutes les réactions complètement négatives, de même que toutes les réactions positives se produisant dans n'importe lequel des trois premiers tubes (dilutions 1:4, 1:8, et 1:16); (2) réactions significatives, qui comprennent toutes les réactions positives se produisant dans le tube N° 4 et au-dessus (dilution 1:32 ou au-dessus).

Une "réaction non significative" avec l'un ou l'autre de ces tests n'exclut pas la tuberculose en activité, car l'observation montre de telles réactions dans approximativement 50% des cas en activité. Toutefois, si une "réaction significative" est obtenue avec l'un ou l'autre de ces tests, la probabilité de l'existence d'une tuberculose en activité est très grande, car il n'y a qu'environ 7% des sujets normaux et seulement approximativement 12 à 14% de sujects présentant une tuberculose pulmonaire stabilisée chez lesquels de telles réactions se sont produites avec la méthode d'hémagglutination comme avec la méthode hémolytique.

Quand les réactions sont interprétées de cette manière, les résultats d'ensemble obtenus avec ces deux méthodes sont comparables. Par contre, les réactions obtenues avec ces tests chez un sujet quelconque ne sont pas nécessairement semblables.

L'usage des deux tests, au lieu du test hémolytique seul, n'apporte aucune aide supplémentaire pour le diagnostic.

Acknowledgment

The authors wish to express their appreciation to Dr. Irving Chapman and Dr. Frederick Zak for their share in supervising the laboratory procedures, and to Mr. Joel Geller and Mr. Joseph Mazesky for their meticulous care in the performance of these tests.

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Case Reports

INTRATHORACIC CYSTS OCCURRING IN A PATIENT WHO HAD RECEIVED OLEOTHORAX[1,2]

WILSON WEISEL AND JOHN D. CONWAY

(Received for publication April 23, 1952)

The recent use of foreign substances in the pleural and extrapleural spaces, particularly the reawakening of interest in mineral oil (1) as a splint within the thoracic cage, has prompted the report of the following case because it may represent an unusual complication of the use of oleothorax.

CASE REPORT

A. F. M., V. A. H. 118 715, a 43-year-old white male, was admitted to the Veterans Administration Hospital, Wood, Wisconsin, on November 17, 1949. He complained of weakness, nonproductive cough, and moderate pain in the right lateral chest which was dull in character and constant in its presence. He had been hospitalized, however, because a routine follow-up gastric culture performed on July 12, 1949 had been positive for *M. tuberculosis*.

On reviewing the patient's previous records and roentgenograms, it was found that he had been diagnosed as having active, moderately advanced, pulmonary tuberculosis in June, 1931, while in the Army. A right artificial pneumothorax had been introduced in August, 1932, for fibrocavitary disease of the right upper lung. The pneumothorax was unsatisfactory, however, because of dense adhesions over the right upper lobe. The pneumothorax was converted to an oleothorax with mineral oil in September, 1932. Review of the old chest roentgenograms showed a density at the base of the right lung consistent with very opaque fluid in September, 1933, and this density appeared encysted and loculated anteriorly over the diaphragm in April, 1934.

The patient had been discharged from another hospital against medical advice in 1934, and he was next examined at this hospital in June, 1947, because of cough and chest pain. Thoracic roentgenograms at that time recorded a fibrotic lesion in the right apex and dense-walled cysts in the right lower lung fields. Repeated examinations of the sputum and gastric contents by smear and culture were negative for tubercle bacilli at that time.

The patient was again referred to this hospital because of a culture positive for tubercle bacilli obtained on a routine follow-up examination of gastric contents on July 12, 1949. On admission to the hospital, smears and cultures of the sputum were positive for *M. tuberculosis*. In addition, thoracic roentgenograms showed a 1 cm. cavity in the right second anterior intercostal space, and the previously noted cystic areas were seen as noted previously (figures 1 and 2).

It was the opinion of the surgical therapy board that the cavitary lesion in the right upper lung was of primary importance in the management of this patient's illness and, because there was no evidence of an acute exudative component, right thoracoplasty was

[1] From the Department of Surgery, Veterans Administration Hospital, Wood, Wisconsin; and Marquette University School of Medicine, Milwaukee, Wisconsin.

[2] Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

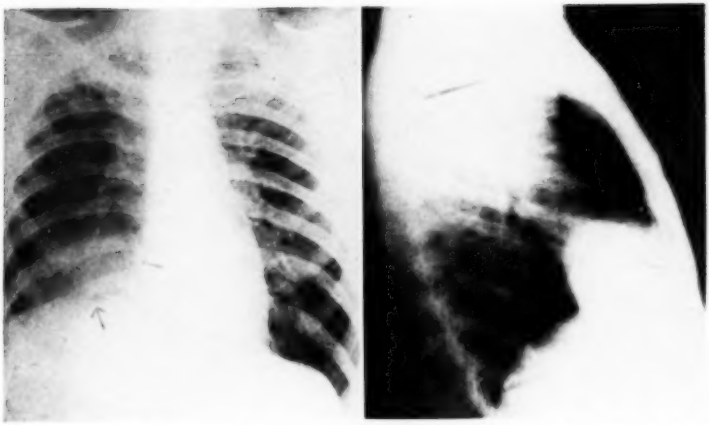

FIG. 1. (Left) Postero-anterior roentgenogram showing rounded densities at base of right chest and fibrocavitary lesions at the right apex.

FIG. 2. (Right) Lateral view showing cystic structure of the right hemithorax.

FIG. 3. Follow-up postero-anterior roentgenogram of the chest after thoracotomy and complete excision of two cysts, showing thoracoplasty and persistent shadow of lesion at right cardiophrenic angle.

recommended. This procedure was begun on December 11, 1949, when the right first and second ribs and adjacent transverse processes were removed as a first-stage thoracoplasty. Four additional ribs were removed in two stages on December 21, 1949, and January 10, 1950. On February 7, 1950, further chest surgery was interrupted temporarily by a perforating diverticulitis of the sigmoid which necessitated emergency abdominal exploration and sigmoid exteriorization.

Following recovery from the acute abdominal episode, it was believed that the intrapleural cystic masses were preventing adequate relaxation of the lesion for which thoracoplasty was being performed. Accordingly, on March 7, 1950, a right thoracotomy (W. W.) was performed after excising the seventh rib and resecting the inferior angle of the right scapula. On entering the pleural space, three distinct cystic masses were found. One was hard, brittle, and attached to the lateral chest wall, the diaphragm, and the surface of the lower lobe. This cyst was easily separated from the adjacent structures and removed. A second cyst, somewhat softer to palpation, was attached to the under surface of the right lower lobe, diaphragm, and posterior lower mediastinum. This cyst was easily separated and removed. A third cyst which was also softer to palpation was found to be firmly adherent to the pericardium, lung hilum, and adjacent mediastinal structures. This cyst wall was not resected because it was believed that its removal would necessitate a major mediastinal dissection and removal of the pericardium. It was the opinion of the surgeon that this lesion had produced no clinical symptoms and, since examination of the previously removed cysts had shown no evidence of neoplastic disease or infection, it was believed that further surgery would unduly increase the operative risk to this patient.

The patient's convalescence from this operative procedure was uneventful. Examination of the gastric contents revealed no evidence of tubercle bacilli on culture. After four months of bed rest following the thoracotomy, the patient was gradually carried through the routine rehabilitation program and discharged as having arrested tuberculosis on March 20, 1951. Follow-up examinations have revealed no clinical symptoms, and roentgenographic studies (figure 3) have shown stability of the tuberculosis, while cultures of the gastric contents have been repeatedly negative for *M. tuberculosis*.

Pathologic Examination

One cyst was hard, noncompressible, and measured 10 by 4 by 5 cm. It was gray to yellowish-white in color, and on section its brittle wall was found to vary from 1 to 4 cm. in thickness. The cyst was filled with a semi-viscid, turbid, gray fluid containing white cream-colored flecks. This fluid had a pH of 7.2, and no peptic activity could be demonstrated. No definite oil particles were seen on examination or after standing to allow layering. The smaller cyst which measured 6 by 5 by 4.5 cm. was similar except that its wall was slightly compressible, but the fluid content was similar.

Microscopic examination of the cysts revealed the walls to be made up of hyaline and partially calcified tissues. There was no evidence of any viable lining in the cysts, and no structures resembling oil droplets were seen in the wall.

COMMENT

The probable association with paraffinomas of the intrapleural cystic lesion described in the patient reported has been deduced from the history that the patient received oleothorax and from the roentgenographic evidence of the appearance of the lesion following this procedure. It should be pointed out, however, that even after careful and special pathologic studies the etiologic connection with mineral oil could not be proved.

In reviewing the literature concerning oleothorax, many complications concerning its use have been described, but the only cases resembling that herein presented have been reported in the French literature. Toussaint and Toussaint (2) in 1949 described three patients who had received oleothorax seventeen months, seven, and eighteen years pre-

vious to the diagnosis of intrathoracic cystic paraffinomas. Two of these patients developed esophageal stenosis and mediastinal compression and the third an intercostal paraffinoma. There have been no cases found similar to the one reported in which the complication of an oleothorax produced cystic lesions which interfered with the surgical collapse procedure.

SUMMARY

A case is reported in which following oleothorax the patient developed intrathoracic cysts which complicated the performance of thoracoplasty for active tuberculosis.

SUMARIO

Quistes Intratorácicos en un Enfermo que Había Recibido Oleotórax

En el caso descrito, el enfermo manifestó quistes intratorácicos después de un óleotórax, lo cual complicó la ejecución de una toracoplastia por tuberculosis activa.

RESUME

Kystes intra-thoraciques survenant chez un malade traité par l'oléothorax

Rapport concernant un cas où le malade a présenté des kystes intra-thoraciques consécutifs à l'oléothorax, ce qui a compliqué l'exécution d'une thoracoplastie pour tuberculose évolutive.

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PNEUMONECTOMY AND STREPTOMYCIN FOR ACUTE STREPTOMYCIN-REFRACTORY PULMONARY TUBERCULOSIS[1,2,3]

With an Illustrative Case Report

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INTRODUCTION

Acute, rapidly progressive pneumonic tuberculosis does not always respond to streptomycin even when the organisms causing the infection are found to be sensitive to the drug. In such circumstances, when the ostensibly "refractory" disease is properly localized, the employment of resection may save life.

In 1943, Overholt and Wilson (1) stated: "Active tuberculosis in the lung, even if it is rapidly spreading, is not a contraindication to resection. In fact, delay may rob these patients of their only chance to get well."

This attitude found expression again in a later report by Overholt and his associates (2) describing 92 resections, of which 42 were done for extensive, predominantly unilateral tuberculosis. Of these 42 patients, "many had rapidly spreading and caseous pneumonic lesions." The exact number with acute pneumonic tuberculosis was not stated, and the therapeutic results for this specific group were not given. Presumably, most, if not all, of these cases were placed in the "desperate risk" category of Overholt for which an operative mortality rate of 41.6 per cent was indicated. The late mortality for this group may be roughly estimated from the rate for the entire series (including both reasonable and desperate risks), which was 41.2 per cent.

The Overholt *et al.* report cited beongs to the pre-streptomycin era. There were those (O'Brien (3) and Maier (4)) who did not accept Overholt's approach to acute, progressive pneumonic tuberculosis. Many undoubtedly agreed with Conklin (5), who believed that, except perhaps as a last resort, resection is contraindicated in acute progressive disease in persons whose condition suggests "marked lack of resistance"—an attitude not very far removed from that of Overholt. Conklin describes his experience before streptomycin was available when, in desperation, he resected "what appeared to be a fulminating terminal tuberculous pneumonia." Despite an early gratifying response, active tuberculosis developed in the remaining lung, with a fatal result.

With the advent of streptomycin, the end results of therapy of this type of tuberculosis have changed notably. It has become common experience to see chemotherapy transform acute pneumonic tuberculosis (acute destroyed lung) into subacute and chronic forms. The use of adequate chemotherapy in the preoperative and postoperative periods has improved both early and late results of pneumonectomy very strikingly in this type of case.

[1] From the Veterans Administration Hospital, Castle Point, New York.

[2] Presented in part at the eleventh Veterans Administration-Army-Navy Conference on the Chemotherapy of Tuberculosis, January 17 to 20, 1952.

[3] Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

In a report on 200 consecutive pulmonary resections, Bailey, Glover, and O'Neill (6) record their experience with 16 cases of acute pneumonic tuberculosis. The first 100 resections, done without the use of streptomycin, included 2 of the 16 patients with acute phthisis. Both of them died. The second 100 patients, treated with streptomycin, included 14 with acute disease. Twelve of these underwent pneumonectomy, and 2 lobectomy. Of the 14 patients, 5 died—a case mortality of 35.7 per cent. Two of the 5 deaths occurred on the operating table as a result of cardiac arrest. The streptomycin regimen varied considerably for the 100 cases. Most of the patients received 1.0 gm. daily for two weeks before, and three weeks after, resection. In "especially acute cases," streptomycin was frequently given in 2.0 gm. daily doses for three to four weeks before, and up to eight weeks after, operation. How many of the acute cases were actively febrile and showing evidence of progressive extension of the disease process at the time of surgery is not stated.

Munz and Adelman (7), in a study of 53 cases of pulmonary resection, report 16 cases of extensive unilateral disease, acute in nature. Each of the 16 patients had streptomycin before surgery for periods varying from 26 to 80 days and averaging, all told, 46.6 days. The dosage was 1.0 gm. daily. Resection was undertaken when it was believed that the patient had obtained the optimum result from antimicrobial therapy. All patients had been febrile prior to the institution of streptomycin therapy. Two patients continued to have low-grade fever at the time of surgery. The remaining 14 were afebrile for periods which varied from 7 to 165 days and averaged 43 days. Of the 16 patients, 3 died—a case mortality of 18.7 per cent. The remaining 13 were alive and well six months to two and one-half years following operation.

A series of 78 resections reported by Sellors and Hickey (8) included 5 pneumonectomies done for acute "destroyed lung" with actively spreading disease. The pneumonectomy was "a measure of despair" in a situation in which the prognosis was otherwise hopeless. Streptomycin was used in all 5 cases, but details regarding responsiveness to chemotherapy and dosage and timing of its administration are not given. Although long-term results had yet to be determined, there were no deaths within six months of surgery, and the immediate results were considered successful. A similar type of experience is mentioned by Laird (9).

Sarot (10), confirming, at least in part, the experience of Conklin, states that febrile and toxic patients tolerate pulmonary resection well and that fever and toxicity abate rapidly after excision unless suppurative complications or spread of disease occur in the postoperative period. He believes that rapidly progressive caseous disease, including progressive primary tuberculosis and caseous lobar pneumonia, should be seriously considered for treatment by resection and mentions the successful performance by Bailey (11) of a pneumonectomy in a two-year-old child for a caseous lobar pneumonia which developed from the rupture of a caseous node into a bronchus.

The employment of resection in an effort to bring about a definitive recovery in progressively invasive, frankly toxic, acute pulmonary tuberculosis showing no response to presumably adequate chemotherapy has not been frequently described in the literature to date. Fossati (12), reporting his experience with resection in pulmonary tuberculosis, refers to acute massive unilobar or unilateral tuberculosis in which the patient's condition deteriorates despite bed rest and streptomycin. Under such circumstances, he believes that immediate resection may be considered and states that in a few cases it has produced brilliant results. Shaw and Paulson (13) have stated: "Massive acute unilobar or unilateral disease in patients whose condition deteriorates rapidly despite rest and streptomycin is becoming an accepted indication for resection." They believe that in some of these patients

a carefully staged thoracoplasty should perhaps be done first. In their opinion it is only in this type of pulmonary tuberculosis that resection may properly be considered a salvage procedure. This discussion contains no description of, or reference to, actual experience with such cases.

In a report of 100 consecutive resections for pulmonary tuberculosis, Jarvis (14) cites 7 cases of acute tuberculous pneumonia with extensive fulminating destruction of one lung. All 7 patients had high fever, marked toxicity, and showed steady clinical deterioration despite intensive chemotherapy. All of these patients also had some active disease in the opposite lung. One of the 7 cases is reported in some detail. Streptomycin was given in a dose of 2.0 gm. daily, without adequate abatement of the progressive invasiveness and toxicity of the disease process until the resection was accomplished. Following resection the temperature dropped abruptly to normal, and rapid improvement followed. A thoracoplasty to replace the pneumothorax was done eight months later. The patient's course was entirely satisfactory one year following surgery. This train of events is cited as essentially characteristic of the 7 cases. The contralateral disease is described as receding satisfactorily in each of these cases. No reference to streptomycin sensitivity determinations is made by Jarvis.

The case reported is essentially similar to those cited by Jarvis. The distinguishing feature of the present report is the record of streptomycin susceptibility studies. The tubercle bacilli present in the sputum prior to operation and in foci of the resected specimen were demonstrated to be susceptible to streptomycin *in vitro*.

CASE REPORT

The patient, a Negro metal polisher, was admitted to Castle Point V.A. Hospital on November 15, 1950, at the age of twenty-seven, with a history of illness of four months' duration. In July, 1950, cough had become manifest and slight loss of weight was noted. One month later his sputum became heavily blood streaked. Subsequently his cough increased, he lost more weight, and experienced feverish and chilly sensations. In the evening of November 15, 1950, he presented himself at Castle Point for admission. He reported a 33-pound loss of weight. He was coughing and raising approximately 15 cc. of mucopurulent sputum. He felt weak, had a poor appetite, and had occasional night sweats. He looked chronically ill, was underweight, and had a temperature of 102.6°F. and a pulse rate of 104. Fluoroscopy showed abnormal densities involving almost the entire left lung. Physical examination of the chest disclosed amphoric breathing and post-tussive rales over the left side.

A blood count showed: 13,500 leukocytes per cu. mm., with 89 per cent mature neutrophils, 7 per cent immature forms, 4 per cent lymphocytes; an erythrocyte count of 4.8 million per cu. mm.; and an erythrocyte sedimentation rate of 28 mm. per hour. The first two sputum concentrate smears were negative and the third was positive for acid-fast bacilli.

The admission film, taken November 17, 1950 (figure 1), was interpreted as showing extensive fibro-ulcerative and exudative disease in the left lung, extending from the apex almost to the base. A 6 cm. cavity was seen in the left apex, with several smaller ones in the lung below. A small linear infiltrate was noted in the lower fourth of the right lung. Otherwise, the right lung was quite clear.

In the two weeks following admission, the patient's temperature increased gradually to approximately 104°F. (oral), rising on two occasions to almost 105°F.

A chest roentgenogram on November 27, 1950 (figure 2), showed serious extension of disease.

On November 29, 1950, streptomycin, 1.0 gm. daily, and *p*-aminosalicylic acid (PAS), 12.0 gm. daily, were started. A drop in temperature was noted the day following institution

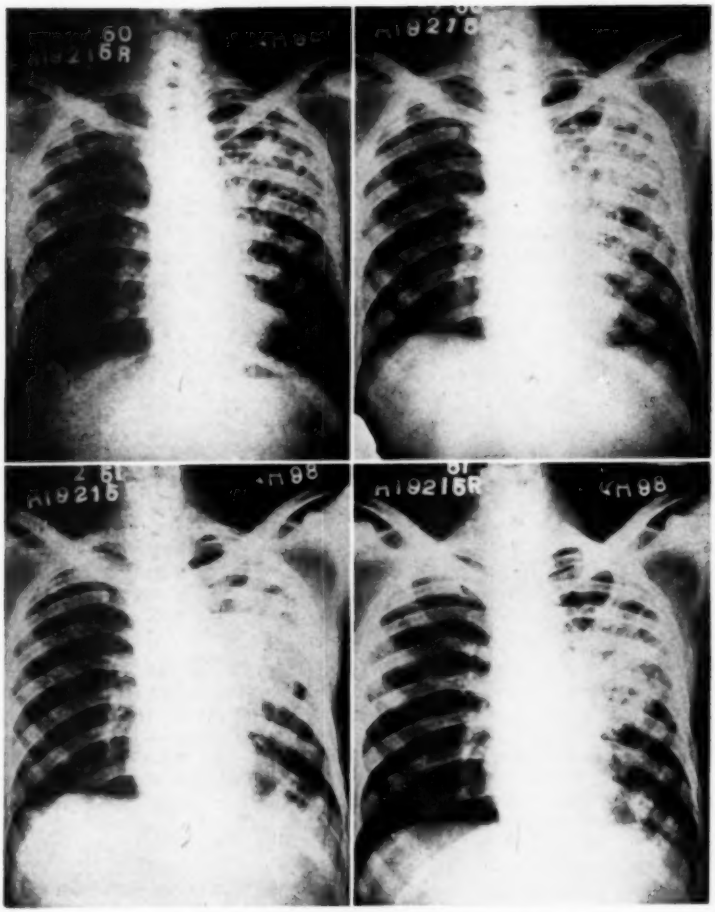

FIG. 1. Roentgenogram taken on November 17, 1950. Approximately 80 per cent of the left lung field is covered by mottled densities consistent with tuberculous infiltration. A 6 cm. cavity occupies a good portion of the upper third. Additional annular shadows, strongly suggestive of cavity, small and medium-sized, are scattered over the upper two-thirds. A linear infiltrate is present on the right, just above the right base. The illustration is somewhat dark, so that the changes at the left base are not well shown.

FIG. 2. Roentgenogram of November 27, 1950, taken just before start of therapy (November 29). There is increased infiltration throughout the entire lung. This is especially marked in the left lower third. The cluster of annular shadows in the lateral aspect of the upper third appears more sharply defined. The details are seen with greater clarity in the original film.

FIG. 3. Roentgenogram taken on January 2, 1951. The cavity formation in the lateral aspect of the upper third and in the lower third has increased in size. There is definite evidence of extension of disease in the left base.

FIG. 4. Roentgenogram taken on January 10, 1951. There is marked increase in excavation, as indicated by enlargement of several areas of rarefaction scattered over the upper three-fourths of the lung field. Additional fresh infiltration is noted in the lower third. There is a suggestion of some clearing at the extreme left base. The small lesion on the right shows no frank change, possibly a slight increase in definition. These changes are seen more clearly in the original film.

of chemotherapy to 101.8°F. and by the second day to 100.8°F. Subsequently, the temperature continued to remain at approximately 101°F. for eleven days and then fluctuated from approximately 100.5° to 103°F.

A chest film taken on January 2, 1951 (figure 3), showed an increase in size of cavity formation in the lateral aspect of the upper third. In addition there was definite evidence of fresh disease at the left base. A preoperative film, taken January 10, 1951 (figure 4), showed further increase in excavation.

FIG. 5. Photograph of resected specimen. The plane in which this section is taken shows three cavities.

Pneumonectomy was performed on January 12, 1951.

On section, the resected specimen showed four cavities, two in the upper lobe and two in the lower (figure 5). Those in the upper lobe measured 5 cm. and 4 cm. in diameter, respectively. Those in the lower lobe each measured approximately 3 cm. in diameter. Both lobes were diffusely consolidated. Scattered throughout the entire lung were flat yellowish and gray caseous foci which varied in size from 5 to 10 mm. Virtually no part of the lung in either lobe was free of this infiltration.

Microscopic examination of the cavity walls and sections of parenchyma uniformly showed evidence of an acute inflammatory process. The cavity walls showed a pyogenic

membrane composed of caseation, polymorphonuclear leukocytes, serum, fibrin, and erythrocytes. Beyond this was a zone of vascular granulation tissue. Surrounding the cavity wall and infiltrating all of the lung parenchyma were many round and oval foci which varied considerably in size and showed extensive central caseation necrosis surrounded by exudative tuberculous granulation tissue. The intervening alveolar spaces showed marked perifocal reaction. Large areas of caseous lobular pneumonia were seen throughout all portions of the lung examined.

The outstanding feature in all of the sections was the marked exudation with no attempt at repair and the absence of fibrosis, fibroblastic proliferation, and collagen formation.

Following resection of the lung, the temperature dropped abruptly to a normal level (figure 6). On the day after the operation, it was noted that the patient appeared nontoxic. The temperature remained normal for thirteen days. A slight subfebrile elevation to 99°F. then appeared. This continued with apparent remissions until the twenty-sixth postoperative day, when signs of bronchopleural fistula became manifest. Drainage and antimicrobial therapy were promptly instituted.

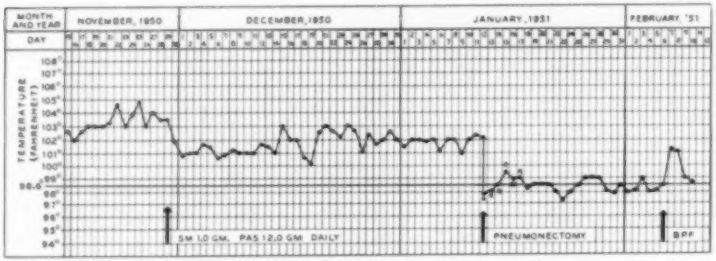

FIG. 6. Record of maximum daily temperature (oral, except as noted) from the day of admission to the twenty-ninth postoperative day. *R*: rectal temperature.

In another ten days there was evidence of secondary infection of the pleural lining of the residual space. Examination of the empyema fluid did not reveal tubercle bacilli but did disclose the presence of *B. proteus*.

On April 3, the first of three stages of a thoracoplasty, undertaken from below up, was done, beginning with the tenth rib. With two-week intervals between stages, the thoracoplasty was completed with an anterior stage on May 3. Recovery was without incident following each stage. Drainage from the pleurocutaneous sinus ceased in July, 1951.

Streptomycin and PAS were given for one full year, terminating December 5, 1951. From November 29, 1950, until January 30, 1951, the eighteenth postoperative day, the patient received 1.0 gm. of streptomycin daily. Thereafter, he received 1.0 gm. twice a week. PAS, 12.0 gm. daily, was given throughout the entire period.

Drug-susceptibility determinations on tubercle bacilli in sputum obtained November 27, 1950, two days prior to the institution of chemotherapy, showed the organisms to be susceptible to streptomycin *in vitro*. The control tube showed ample growth at the thirty-fifth and forty-second days; no growth appeared in the tubes containing, respectively, 3.5, 15, and 200 γ of streptomycin per ml. In addition, organisms from each of two foci in the pathologic specimen, one in each lobe, were found to be equally susceptible to streptomycin. The susceptibility of the tubercle bacilli to PAS was not determined.

At the present time, the patient is well and is without symptoms. There is no cough. Sputum is minimal in amount and has been consistently negative for tubercle bacilli by smear and culture since the pneumonectomy. The last chest film, taken March 6, 1952, shows an essentially normal remaining lung (figure 7). A bronchoscopic examination

performed on November 19 showed a clean, well-healed main bronchial stump. A blood count done on March 14, 1952, gave normal findings. The erythrocyte sedimentation rate was 2 mm. per hour. No toxic effects from the chemotherapy have been noted. The patient's hearing capacity was tested by audiogram before chemotherapy and found to be moderately impaired. No added impairment resulted from the streptomycin. The last audiogram was obtained on January 24, 1952, and is essentially the same as the one obtained before the start of treatment. Vestibular function is likewise intact. The patient was transferred from the infirmary to the semi-ambulatory ward on January 28, 1952. He now weighs 162 pounds, 27 pounds above his weight prior to surgery.

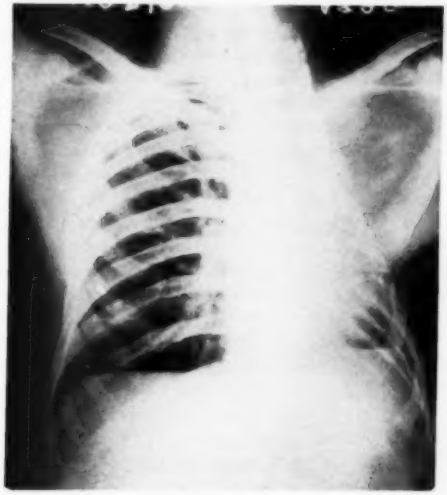

FIG. 7. Roentgenogram taken on March 6, 1952. The remaining lung is clear except for the linear and nodular shadows in the lower fourth of the lung. These have been quite discretely outlined for well over a year.

COMMENT

One characteristic feature of this case in common with those cited by Jarvis (14) is the progressive invasiveness of the tuberculous process in the six weeks following the institution of a first course of streptomycin and PAS therapy, administered in what is generally considered continuous adequate daily dosage. Except for a slight reduction in the maximum daily temperature to approximately 101° F. (a reduction sustained approximately eleven days) from a previous average maximum daily temperature of 103°F. (oral), the chemotherapy had no appreciable influence on the course of the disease. Three chest films covering the six-week period showed progressive extension of the disease process. The invading organisms were susceptible to streptomycin, as indicated by three sets of direct drug-susceptibility studies: one on tubercle bacilli in sputum obtained prior to operation and one each on bacilli in caseous material obtained from two foci in the resected lung.

The explanation for the lack of response to chemotherapy in an infection in which the

organisms are susceptible to streptomycin deserves serious attention. This phenomenon is apparently not uncommon, as indicated by the experience of Jarvis (14) and also that of Fossati (12). Depending on the sources of patients and on admission procedures, certain institutions may well see more of these cases than others. Such acute "streptomycin-refractory" pulmonary tuberculosis, in which the infecting organism is found to be susceptible to streptomycin, seems to be related to the amount of tissue involved in the rapidly invasive process. In this case, a period of three months elapsed between the time of the first appearance of serious symptoms (heavily blood-streaked sputum) and the administration of the first doses of streptomycin and PAS. The writers' experience to date with chemotherapy in tuberculosis would make it unreasonable to assume that the patient would have been refractory to streptomycin throughout this entire period. Obviously, too, the influence of dosage on this clinical phenomenon also deserves consideration. At any rate, this experience must, for the time being, be interpreted as indicating that acute pneumonic tuberculosis with high fever and toxicity is a clinical emergency calling for the immediate institution of adequate chemotherapy.

The second important feature of this case, also noted in the cases of Jarvis, is the abrupt drop in temperature and the sustained improvement in the patient's general condition which followed so quickly after the removal of the diseased lung. This critical change illustrates most dramatically the urgent nature of the clinical problem and the extreme importance of the timing of therapeutic procedures. Had the surgery been delayed, a spread of tuberculosis to the opposite lung with the emergence of a drug-resistant infection might well have occurred and made resection still more hazardous or even impossible.

SUMMARY

A case illustrating the apparent advantages inherent in the employment of early resection combined with chemotherapy in unilateral toxic progressive caseous lobular pneumonia, refractory to streptomycin and PAS therapy, when used alone, has been reported. Throughout the entire six weeks of chemotherapy prior to operation, the patient ran a severe febrile course. Consecutive films showed steadily advancing involvement and destruction of the lung until resection was performed. Tubercle bacilli from the sputum and from tuberculous foci in the resected specimen were susceptible to streptomycin *in vitro*. The resected lung showed multiple cavitation and practically total involvement in a caseous lobular pneumonic process. Following pneumonectomy, the toxicity of the illness suddenly abated and the temperature became normal within twenty-four hours. This improvement was sustained for twenty-six days. Bronchopleural fistula and empyema then appeared and were treated by drainage and thoracoplasty. Recovery followed promptly. Chemotherapy was maintained for one year. The patient remains well, one year and two months following pneumonectomy, ten months following multiple-stage thoracoplasty.

This case and those recorded by Jarvis tend to support the following conclusions:

In the presence of sufficient involvement, sustained progression may occur in acute pneumonic tuberculosis despite treatment with daily dosage of 1.0 gm., or even 2.0 gm., of streptomycin and 12.0 gm. of *p*-aminosalicylic acid in a previously untreated patient with drug-susceptible tubercle bacilli.

Despite intense activity of a tuberculous process and severe toxicity resulting from it, removal of tuberculous tissue, when associated with adequate chemotherapy, may result in recovery.

There may be a phase in the development of acute tuberculous caseous lobular pneumonia when the institution of chemotherapy is a matter of extreme urgency.

In the treatment of such cases, consideration should be given to increasing the dosage of streptomycin beyond the customary 1.0 gm. daily.

SUMARIO

La Neumonectomía y la Estreptomicina en la Tuberculosis Pulmonar Aguda Estreptomicinorresistente

Después de discutir el tratamiento de la tisis unilateral aguda, preséntase, como ejemplo, un caso de neumonía lobular caseosa evolutiva tóxica que invadía casi todo el pulmón izquierdo y revelaba grandes cavernas múltiples. Durante las seis semanas enteras de quimioterapia antes de la operación, el enfermo mostró una grave evolución febril. Las radiografías tomadas consecutivamente revelaron constante avance de la invasión y destrucción del pulmón hasta que se ejecutó la resección. Los bacilos tuberculosos obtenidos del esputo y de los focos tuberculosos del ejemplar resecado fueron sensibles a la estreptomicina. A continuación de la neumonectomía la toxicidad cedió repentinamente y la temperatura se normalizó en término de veinticuatro horas. Esta mejoría se sostuvo por espacio de veintiséis días. Luego aparecieron fístula y empiema broncopleurales que fueron tratados con la canalización y la toracoplastia. La reposición sobrevino rápidamente. La quimioterapia fué mantenida un año. El enfermo sigue bien, al año y dos meses de la neumonectomía y a los diez meses de una toracoplastia en varios tiempos.

Este caso y los comunicados por Jarvis tienden a apoyar las siguientes conclusiones:

En presencia de suficiente invasión, puede haber agravación sostenida en la tuberculosis neumónica aguda a pesar del tratamiento con dosis diarias de 1.0 gm. y hasta 2.0 gm. de estreptomicina y 12.0 gm. de ácido para-aminosalicílico (PAS) en un caso que mostraba microbios sensibles al ser tratado primitivamente.

Bajo la protección de la estreptomicina y del PAS, a pesar de la intensa toxicidad y actividad del proceso, la resección del tejido enfermo puede ir seguida de la reposición.

Puede haber una fase en el desarrollo de la neumonía lobular caseosa tuberculosa aguda en la que la institución de la quimioterapia cobra suma urgencia. En el tratamiento de dichos casos, hay que considerar el aumento de la dosis de estreptomicina a más allá del habitual 1.0 gm. diario.

RESUME

Pneumectomie et Streptomycine dans la tuberculose pulmonaire aiguë streptomycino-résistante

Les auteurs présentent un cas type de pneumonie lobulaire caséeuse toxique et évolutive interessant la presque totalité du poumon gauche. Pendant toute la période de six semaines de la chimiothérapie préopératoire, le malade présentait un état fébrile sévère. Des radiogrammes successifs montraient un processus évolutif constant et la destruction du tissu pulmonaire, jusqu'au moment où la résection pulmonaire a été effectuée. Les bacilles tuberculeux provenant des crachats et des foyers tuberculeux obtenus par résection étaient sensibles à la streptomycine. A la suite de la pneumectomie les phénomènes toxiques se sont affaiblis et la température est redevenue normale dans les vingt quatre heures. Cette amélioration s'est maintenue pendant vingt six jours. Il s'est alors produit une fistule broncho-pleurale et de l'empyème; un traitement par drainage et thoracoplastie a été instauré et la guérison a été rapide. La chimiothérapie a été poursuivie pendant une année. L'état du malade est demeuré bon pendant un an et deux mois après la pneumectomie et dix mois après les temps successifs de la thoracoplastie.

Ce cas, de même que ceux de Jarvis, tendent à confirmer les conclusions suivantes:

Quand le processus pathologique est suffisamment marqué, une progression continue peut se manifester dans la pneumonie tuberculeuse aiguë en dépit d'un traitement avec des doses quotidiennes de 1 gramme ou même de 2 grammes de streptomycine et de 12 grammes d'acide para-aminosalicylique (PAS) comme dans

une observation originale de traitement d'un cas comportant des bacilles résistants.

Grâce à la protection offerte par la streptomycine et le PAS, en dépit de phénomènes toxiques marqués et de l'activité du processus, l'exérese des tissus lésés peut permettre la guérisson.

Dans la tuberculose pulmonaire il peut y avoir une phase de l'évolution de la pneumonie caséeuse lobulaire aiguë, au cours de laquelle l'instauration de la chimiothérapie est d'une extrême urgence. Dans le traitement de tels cas, il y a lieu d'envisager l'élévation de la dose quotidienne à une valeur supérieure à 1 gramme, qui est celle de la dose quotidienne classique.

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Editorial

Effect of Isoniazid on the Program of the Tuberculosis Association[1]

Since the public health implications of isoniazid necessarily depend upon the clinical and laboratory data, it may be well first to summarize briefly and simply some of these data concerning isoniazid:

Isoniazid is a chemical which is easily synthesized; will be cheap in cost, when released by the Food and Drug Administration for sale on physicians' prescriptions;[2] and will be available in large supply, since numerous drug companies in this country and abroad are manufacturing the drug.

The drug has been found to be effective against tubercle bacilli in the test tube and in tuberculous infections in experimental animals, even when there is considerable delay in starting treatment with the drug following infection of the experimental animal.

If treatment is continued for only three or four months in such experimental animals and then discontinued, relapses occur.

Virulent tubercle bacilli have been grown from small, residual pulmonary lesions removed at autopsy of killed experimental animals (guinea pigs and rabbits), which apparently had recovered following intensive and prolonged treatment with the drug.

Isoniazid behaves well pharmacologically in man. Upon administration by mouth in suitable dosages, concentrations of the drug are obtained in the plasma and in the cerebrospinal fluid which are highly effective against virulent human tubercle bacilli in the test tube and yet well below concentrations found to be toxic in experimental animals. At such dosages, no serious toxicity has been encountered thus far.

Improvement, sometimes dramatic, from the standpoint of increased appetite, gain in weight, and reduction of fever frequently occurs when patients with far advanced caseous-pneumonic disease are treated with the drug. Changes in the chest roentgenogram have not been notable, but the films were of patients with extensive tissue destruction. In cases of miliary tuberculosis, impressive improvement has occurred during isoniazid treatment, including marked clearing in serial chest roentgenograms. However, only a few such patients have been treated thus far and treatment in these patients has been carried on for only a few months. The ultimate benefit in both types of patients and in other types and stages of tuberculosis awaits further experience.

Isoniazid appears to have certain advantages over streptomycin and para-aminosalicylic acid (PAS) because of anticipated cheapness and low toxicity; because administration is by mouth, rather than by hypodermic injection, in contrast with streptomycin; and because of absence of irritation of the gastrointestinal tract, in contrast with PAS. It seems doubtful, however, that, from a purely therapeutic standpoint, isoniazid will prove to be markedly superior to the already very effective combination of streptomycin and PAS.

Similar to the experience with streptomycin, strains of tubercle bacilli which are resistant to the action of the drug appear in the sputum of patients under treatment.

From the public health standpoint, the first point to be made is that the new

[1] Presented before a Special Session, as part of a symposium on *Isonicotinic Acid Derivatives in Tuberculosis Treatment*, at the 48th annual meeting of the National Tuberculosis Association, Boston, Massachusetts, on May 26, 1952.

[2] Released on June 4, 1952.

drug is not a preventive, but at best only a better method of treatment of a patient who already has developed tuberculous disease. There is no reason to believe at present that the drug will be administered to persons to prevent the development of tuberculous disease.

One must not assume that there will be a decline in tuberculosis as the result of the development of these new drugs comparable with the decline in prevalence of, say, pneumococcal pneumonia, following the development of effective chemotherapeutic agents against pneumococcus. Pulmonary tuberculosis and pneumococcal pneumonia have significantly different characteristics. Pneumococcal pneumonia is an acute infection usually ushered in with severe and dramatic symptoms and signs and, even in the absence of specific therapy, usually quickly terminates either in death or recovery, and, if recovery, without residual tissue destruction. Pulmonary tuberculosis, on the other hand, is characterized in the average case by a symptomless onset, making diagnosis difficult in the early stages and before the infection has been passed on to others. It is characterized by the development of caseation necrosis and tissue destruction which is often extensive. It is characterized by chronicity and relapses.

In view of these characteristics, it seems unlikely that even a greatly improved drug will exert a rapid effect on the prevalence of tuberculosis, even though it should help to accelerate control of tuberculosis in the long run, if other proved effective control measures are not reduced or abandoned as the result of unjustified optimism regarding the role of the drug itself.

The second point is that there seems to be no reason to assume that the new drug will change the *nature* of the tuberculosis control program any more than streptomycin and PAS changed the nature of the program.

Since the time when streptomycin and PAS became available:

There has been an intensification of case-finding procedures. The more effective the tools we have in the treatment of tuberculosis, the more reason we have for finding cases; and at as early a stage as possible. Furthermore, knowledge that there is available effective therapy should stimulate better cooperation on the part of the public in such case-finding programs.

There has been no reduction in the need for hospital beds for tuberculous patients. The average duration of hospital stay has not decreased. Although patients whose disease has been detected in its early stages may have a shorter stay in the hospital, this is compensated for by the prolonged stays of those patients who would have died quickly from the disease if the improved treatment had not resulted in prolonged illness, instead of rapid death. Furthermore, more extensive use of surgical procedures, made possible by using streptomycin to control the spread of infection in the lungs during and after surgery, also has resulted in greater rather than fewer demands upon hospital facilities. Finally, tuberculosis is an infectious disease, and segregation of infectious tuberculous patients in hospitals is necessary to protect others. Many patients continue to be infectious despite prolonged and intensive treatment with the new, as well as older, drugs.

There has been no decrease in need for rehabilitation. Here, again, the possibility of a drug's permitting shorter periods of hospitalization in early cases, and thus reducing the rehabilitation problem, is balanced by the needs of the patients at the other end of the spectrum who suffer from a prolonged illness with ultimate recovery, instead of what otherwise would have been a rapidly fatal disease.

There has been no reason to decrease the program of research. Streptomycin and PAS, and isoniazid, are not perfect drugs. Research must go on and is going on for even better ones.

Furthermore, a good *vaccine*, superior to BCG, would have greater potentialities for more rapid control of tuberculosis than any method of *treatment*.

In addition to purely medical research, social and economic factors, including nutrition, still need further study and definition of their relative roles in the tuberculosis problem, with the possibility of more effective practical application when these factors are more precisely defined.

There has been no reduction in the program of education. Underlying and essential to all aspects of the tuberculosis control program is an adequate program of education of both the general public and members of the medical and allied professions. The need for such a program was as necessary after streptomycin and PAS became available as it was before. In view of the distorted impressions concerning isoniazid acquired by millions of people through the original premature sensational reports in the newspapers, the educational program not only must be continued but must be intensified.

Isoniazid could actually prove a temporary step backward, *if*:

> the drug is used indiscriminately by physicians on ambulatory patients who could be hospitalized, with spread of the infection from these patients to others and with development of widespread strains of tubercle bacilli resistant to the drug;
> patients refuse other indicated treatment, such as surgery, because of unjustified faith in effectiveness of the drug;
> there is an unjustified decrease in funds for tuberculosis control programs, with reduction of emphasis or abandonment of other proved effective methods of control.

The comments thus far have applied to the tuberculosis control program as a whole, and do not distinguish between those aspects particularly pertinent to the program of the voluntary tuberculosis association in contrast with those pertaining to the official health agency.

My special assignment has been to comment on the effect on the program of the tuberculosis association. Such differentiation necessarily involves a consideration of the difference between the program of the voluntary agency and that of the official agency.

Actually, with the exception of enforcement of laws and regulations, there is no aspect of the tuberculosis control program which, under an appropriate set of local conditions, cannot be engaged in legitimately by the tuberculosis association, at least on a temporary, demonstration basis. It is generally agreed, however, that the tuberculosis association's special usefulness lies in the field of education.

The tuberculosis association can be particularly effective in this field because it consists of medical and non-medical citizens of the community, brought together on a volunteer basis solely because of their interest in the control of tuberculosis. Hence, statements from these volunteers to their fellow citizens and to the legislative representatives of their communities are likely to carry greater weight than statements from employees of health departments.

Tuberculosis associations, therefore, must assume the major role in preventing,

on the one hand, misinterpretation of the part a new drug will play in the tuberculosis control program; and, on the other hand, seeing to it that the full potentialities of an improved method of therapy are incorporated in the control program as quickly and as widely as possible within the limits of sound practice as indicated by scientific appraisal.

Some of the ways tuberculosis associations may assume and have assumed this role are as follows:

Authoritative statements on the current experimental and clinical evaluation of the drug are issued as needed by the medical section of the National Tuberculosis Association, the American Trudeau Society. These statements are prepared in their original drafts by committees of highly qualified scientists and formally approved in final form by the Executive Committee or Council of the ATS.

The secretariat of national, state, and local associations see that such statements reach promptly all those who need to be kept currently informed of technical progress, such as members of the medical profession, health department personnel and staff, and board members of tuberculosis associations. This is accomplished through news letters, publication in professional journals and association bulletins, papers presented at annual meetings, discussions at postgraduate courses, work conferences and staff conferences, and by other means.

The tuberculosis associations must see that representatives in government responsible for appropriations for tuberculosis control programs of national, state, and local official health agencies are accurately informed of the true implications of the new drug therapy, and they must attempt to get such appropriating bodies to restore necessary funds if a mistaken impression of the value and role of the new drug has resulted in unwarranted reductions in appropriations.

Guided by statements from the American Trudeau Society, tuberculosis associations should use all types of publicity media to keep the general public currently informed of the true role of the new drug so that the public will support, through personal cooperation and through providing the necessary funds, an intensification rather than a reduction in the case-finding and other aspects of the tuberculosis control program of both the official and voluntary health agencies.

In summary: Isoniazid gives promise of being another very helpful tool in the treatment of tuberculosis, although it will be some time before we can accurately assess its value.

There is no reason to assume that it will change the *nature* of the attack on the tuberculosis problem any more than have streptomycin and PAS.

The availability of any improved method of treatment demands an intensification of case finding, hospitalization, rehabilitation, research, education, and all other aspects of the tuberculosis control program so as to take full advantage of the improved method of treatment.

Tuberculosis associations, because of the nature of their organization and manner of functioning, must assume a major role in preventing or correcting misinterpretations of the role of new drugs and in ensuring the most effective utilization of these improved methods of treatment in advancing the tuberculosis control program as a whole.

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Notes

PATIENT TOLERANCE FOR CALCIUM SALT OF PARA-AMINOSALICYLIC ACID: PRELIMINARY REPORT

Para-aminosalicylic acid (PAS) has been established as an effective bacteriostatic agent by many studies since the initial report by Lehmann[1] in 1946. Its great usefulness in effecting a delay in the emergence of organism resistance during combined therapy with streptomycin and PAS, as shown by Tempel and co-workers,[2] has made the problem of the gastrointestinal irritation caused by this substance of great importance. It is known, as reported by Bogen and associates,[3] that the irritating effects of the sodium salt of PAS are highly variable both within the same batch and between different batches of the same drug. Furthermore, a considerable number of patients are not able to tolerate the sodium salt either in adequate dosage or during prolonged treatment. In 1950, Disler[4] reported that the calcium salt of PAS, in doses of 4.0 gm. three times daily, gave adequate blood concentrations; in fact, better than those obtained with the sodium salt of PAS in doses of 3.0 gm. four times daily. In an attempt to find a more readily tolerated form of PAS, the calcium salt[5] is being studied at this hospital.

The present investigation was carried out on patients in the National Jewish Hospital at Denver who were undergoing combined treatment with streptomycin and PAS. The patients were all treated on a routine course of streptomycin, 1.0 gm. every third day, and the sodium salt of PAS, 3.0 gm. four times daily, for a total duration of at least four months. The single criterion for the selection of patients for trial on the calcium salt of PAS was that the patient was unable to tolerate the usual form of the sodium salt of PAS prepared in the routine manner. This intolerance was invariably manifested by some form of gastrointestinal irritation, such as abdominal distress, nausea, vomiting, diarrhea, colicky abdominal pain, or by any combination of these complaints. If, during the course of treatment, the signs and symptoms of gastrointestinal irritation appeared to become severe enough, the PAS was discontinued for a few days, and then it was resumed. When it became clear that the irritation was due to the sodium salt of PAS, then the calcium salt was substituted in its place, the dosage being 5.0 gm. three times daily. If the calcium salt was not well tolerated, the patients were once more treated with the sodium salt in order that some evaluation of the relative irritating effect of the two substances could be arrived at.

Twenty-four patients who reacted adversely to the sodium salt of PAS were studied; 18 were females, 6 were males. It was found that 13 of the patients, while on the calcium salt of PAS, were completely free from the symptoms which had necessitated the change. In addition, 4 patients were noted to have occasional mild bouts of gastrointestinal irritation while on calcium salt. This was not so severe as to result in a reduced dosage or interruption of their course of treatment. Thus, 17 of the 24 patients who had demon-

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[2] Tempel, C. W., Hughes, F. J., Mardis, R. E., Towbin, M. N., and Dye, W. E.: Am. Rev. Tuberc., 1951, *63:* 295.

[3] Bogen, E., Loomis, R. N., and Will, D. W.: Am. Rev. Tuberc., 1950, *61:* 226.

[4] Disler, M.: Schweiz. Ztschr. Tuberk., 1950, 7, fasc. 6.

[5] The calcium salt of para-aminosalicylic acid (Pasara Calcium Granulate) was supplied for this investigation by Smith-Dorsey, a division of the Wander Company, in the form of granules coated with a sialoresistant substance.

strated that they could not tolerate the sodium salt of PAS were able to take the calcium salt without the appearance of serious symptoms or signs. Two patients found the calcium salt to be more irritating than the sodium salt of PAS and again were given the sodium salt. At this same time 3 patients were totally unable to tolerate any form of PAS, apparently on the basis of an incipient chronic ulcerative colitis. The sialoresistant coated granules of the calcium salt of PAS which were used in this study were found to be tasteless and very easy for patients to take. However, 2 patients with dentures of the fixed type found that the granules tended to lodge in the crevices of their dentures and that, eventually, the coating substance dissolved. The end result for these patients was more intolerable than the sodium salt of para-aminosalicylic acid.

Tempel and co-workers[3] have clearly shown that, during the course of discontinous streptomycin therapy (every third day), the daily use of PAS in adequate dosage results in a markedly lowered incidence of the appearance of human tubercle bacilli which are resistant to either drug. Therefore, it becomes of considerable importance to find a form of PAS which can be tolerated by patients with a minimum of gastrointestinal irritation.

The advantages of the calcium salt of PAS are that it is easier to take and more palatable. This allows the patient to take a more adequate dosage of the drug. In addition, as was shown by Disler,[4] the maximum blood concentrations are higher and of longer duration with the calcium salt than with the sodium salt. Furthermore, in the group of patients with incipient cardiac decompensation where the low sodium diet is of extreme importance, the calcium salt of PAS should be superior to the sodium salt. Exactly the same thing is true for such patients as those in whom renal failure is impending and in those with marked hypoproteinemia. In these cases, while the problem of calcium excretion through the kidney is important, the relative reduction in the sodium intake resulting from the use of the calcium salt should be of very great value.

In summary: Tolerance for the calcium salt of para-aminosalicylic acid as compared with the sodium salt of para-aminosalicylic acid was investigated in 24 patients who developed severe gastrointestinal irritation from the latter preparation. In this group of 24 patients who reacted with severe gastrointestinal symptoms to the sodium salt, 13 were symptom free on the calcium salt and 4 had only mild symptoms of gastrointestinal irritation. Therefore, 17 of this select group were definitely more able to tolerate the calcium salt of PAS than the sodium salt. On the other hand, 2 patients found the calcium salt more irritating than the sodium salt of PAS, and 3 were completely unable to tolerate PAS in any form. It was found that fixed dentures constituted a handicap to the proper use of the granulate form of the calcium salt of para-aminosalicylic acid.

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AN EVALUATION OF THE COMPLEMENT-FIXATION MODIFICATION (MAILLARD) OF THE HEMAGGLUTINATION TEST IN TUBERCULOSIS[1]

With the advent of the hemagglutination test for antibodies against tubercle bacilli, hopes were raised that this would aid either in the diagnosis or in the estimation of prognosis of the disease. Reports from numerous laboratories[2, 3, 4] have failed to support this

TABLE 1

COMPLEMENT-FIXATION TEST
COMPARISON OF TITERS FROM TUBERCULOUS AND NONTUBERCULOUS PATIENTS

DONORS	TOTAL NUMBER OF PATIENTS	NO REACTION		TITERS									
				1	2	3	4	5–10	11–15	16–20	21–25	26–30	30 plus
Normal controls	38	20	(52%)	4	4	1	2	3	2				2
Inactive pulmonary tuberculosis (1 to 10 yrs.)	58	7	(12%)	2	5	2	3	13	6	6		3	11
Active pulmonary tuberculosis	67	8	(12%)										
Minimal	13	2					3	3		1	1	1	2
Moderately advanced	26	4		2	3		2	5	6				4
Far advanced	28	2			1	1	4	4	1	1	3	1	10

TABLE 2

COMPARISON OF HEMAGGLUTINATION TEST AND COMPLEMENT-FIXATION TEST FOR TUBERCULOSIS

NORMAL CONTROLS*				ACTIVE TUBERCULOSIS†‡			
Hemagglutination Test	Complement-Fixation Test			Hemagglutination Test		Complement-Fixation Test	
Negative; less than 1:8	18 (58%)	Negative	20 (52.6%)	Negative	6 (18.7%)	Negative	2 (6.2%)
Doubtful; 1:8	7 (22.5%)	Titer 1:3	9 (23.6%)	Doubtful	7 (21.8%)	Titer 1:3	2 (6.2%)
Positive; more than 1:8	6 (19.5%)	Titer 4 or more	9 (23.6%)	Positive	19 (59%)	Titer 4 or more	28 (87.5%)

* Twenty-two of the sera used were the same in both tests while in nine cases, separate sera specimens were used.
† Identical sera used in both tests.
‡ These were practically all far advanced cases.

hope. More recently, Maillard and Gagliardo[5, 6] have devised a modification of the complement-fixation test described by Middlebrook[7, 8]. They have claimed that more quan-

[1] This study was aided, in part, by a grant from the Westchester Tuberculosis and Health Association.

[2] SPAIN, D. M., CHILDRESS, W. G., AND ROWE, C.: Am. J. Clin Path., 1952, *22*, 86.
[3] FLEMING, J. W., RUNYON, E. H., AND CUMMINGS, M. M.: Am. J. Med., 1951, *10*, 704.
[4] SMITH, D. T., AND SCOTT, N. B.: Am. Rev. Tuberc., 1950, *62*, 121.
[5] MAILLARD, E. R., AND GAGLIARDO, F. J.: Am. Rev. Tuberc., 1951, *64*, 675.
[6] MAILLARD, E. R.: Am. J. Pub. Health, 1952, *42*, 175.
[7] MIDDLEBROOK, G., AND DUBOS, R. J.: J. Exper. Med., 1948, *88*, 521.
[8] MIDDLEBROOK, G.: J. Clin. Investigation, 1950, *29*, 1480.

titive results were obtained with their modification. The purpose of the present paper is to report an evaluation of the Maillard-Gagliardo modification of the Middlebrook serologic test in tuberculosis.

Using the procedure developed by Maillard and Gagliardo[5], a series of tests were done on 163 persons. Sixty-seven of the group had active pulmonary tuberculosis which was classified either as minimal, moderately advanced, or far advanced. All 67 were hospitalized patients at Grasslands Hospital. Fifty-eight patients had inactive tuberculosis for periods ranging from one to ten years. The classification of inactivity was based upon sputum cultures repeatedly negative for *M. tuberculosis*, stable roentgenographic findings, and no symptomatic or other laboratory evidence of active disease. For the most part, these persons were all being followed in the Outpatient Department. Thirty-eight persons were regarded as normal controls and were all personnel employed in the Laboratory Department. In 32 of the patients with active tuberculosis, Middlebrook hemagglutination tests were also performed. The same was done with 31 of the controls.

In each group (table 1), including the controls, the titer was spread over the complete range from negative to titers greater than 30. There was a general shift to the higher titers in patients with active tuberculosis, especially those with far advanced disease. The normal control group contained a greater number of negatives, while in the clinically inactive group the titers were rather evenly distributed over the entire range.

In a smaller group, a comparison was made between the original hemagglutination test of Middlebrook and the Maillard modification of the complement-fixation test. As is shown in table 2, neither test is more effective for the determination of the presence or activity of tuberculosis. A general trend was observed in both tests so that there was a greater percentage of negative reactors in the control group and a greater percentage of positive reactors, including those with higher titers, in the tuberculosis group. The findings in the present report are at variance with the results obtained by Maillard[5, 6], particularly with regard to the normal control group, in which positive titers were obtained in 18 of 38 persons in the present study, whereas Maillard did not obtain a single positive reaction among 48 normal controls. In general, it was found that the latter modification did not result in any significantly better quantitive results than those obtained with the original hemagglutination procedure described by Middlebrook and Dubos.

In summary: Studies with the Maillard and Gagliardo modification of a complement-fixation test and a hemagglutination test in tuberculosis revealed no significant advantage of the former over the latter. The complement-fixation procedure is still not sufficiently accurate to be used routinely either for the detection of tuberculosis or for the evaluation of activity of the disease.

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STUDY OF CULTURE FILTRATES OF PATHOGENIC FUNGI AND YEASTS FOR TUBERCULOSTATIC PROPERTIES[1]

In the search for better antibiotic substances, many laboratories are screening organisms of many sorts. Most of this work involves the study of saprophytes. There have been no reports concerning the pathogenic fungi and yeasts in terms of possible production of substances with tuberculostatic activity.

The fungi and yeasts in list 1 were grown in quantity and their culture filtrates were tested for inhibitory activity.

List 1

Fungi from which filtrates were produced and tested against tubercle bacilli. Those marked were also tested against organisms in list 2*

1. *Trichophyton faviforme* var. *ochraceum*
2. *Trichophyton faviforme* var. *alba*
3. *Trichophyton rubrum**
4. *Trichophyton mentagrophytes**
5. *Trichophyton violaceum**
6. *Trichophyton concentricum*[2]
7. *Trichophyton ferrigineum*
8. *Trichophyton sabaraudi*
9. *Microsporon fulvum**
10. *Microsporon audouini**
11. *Microsporon canis*
12. *Candida albicans*
13. *Candida tropicalis**
14. *Candida krusii**
15. *Candida stellatoidea**
16. *Candida guillermondi**
17. *Candida parasilassi*
18. *Geotrichoides krusii*
19. *Nocardia asteroides*[2]
20. *H-K unclassified*
21. *Nocardia madurae*
22. *Mycobacterium smegmatis*

While the primary interest was in possible tuberculostatic substances, those filtrates marked with an asterisk in list 1 were also tested against the organisms in list 2. The filtrates so tested against the organisms in list 2 had been stored for varying periods at 5°C.[3]

List 2

1. *Bacillus subtilis*
2. *Escherichia coli*
3. *Klebsiella pneumoniae*
4. *Staphylococcus aureus*
5. *Streptococcus hemolyticus*
6. *Aerobacter aerogenes*
7. *Pneumococcus*, type 1
8. *Salmonella paratyphi A*
9. *Shigella flexneri*
10. *Salmonella typhi*
11. *Streptococcus fecalis*
12. *Neisseria catarrhalis*
13. *Salmonella paratyphi B*
14. *Brucella abortus*
15. *Shigella dysenteriae*
16. *Streptococcus viridans*
17. *Bacillus anthracis*
18. *Proteus vulgaris*
19. *Corynebacterium diphtheriae*

Many of the pathogenic fungi are rather difficult to grow in quantity with any degree of rapidity, and considerable experimenting was done before the culture medium for the production of filtrates was finally adopted.

[1] This study was aided, in major part, by a grant from the Committee on Medical Research of the American Trudeau Society, medical section of the National Tuberculosis Association; and, in part, by a grant from the Committee on Medical Research of the University of Pennsylvania.

[2] Some filtrates active against tubercle bacilli (*see* text).

[3] The testing of the filtrates against the organisms in list 2 was done by Eugene L. Gehry in the laboratory of Dr. Ben Boltjes at the Medical College of South Carolina.

With slight modifications in a few specific instances, the composition of the growth medium for the fungi and yeasts was as follows:

Sodium nitrite	3.0 gm.
Dibasic potassium phosphate	1.0
Magnesium sulfate	0.5
Potassium chloride	0.5
Ferrous sulfate	0.05
Calcium carbonate (micro-powder)	3.0
Zinc sulfate	0.002
Copper sulfate	0.002
Manganese chloride	0.005
Dextrose	35.0
Maltose	35.0
Bacto yeast extract	1.0
Protolysate (Meade Johnson)	10.0
Glycerin	20.0
Distilled water	1,100.0 ml.

In this medium most of the cultures grew rapidly. It was necessary to vary the period of growth, depending on the organism. Most cultures were filtered at fourteen days, when heavy growth was obvious. Some required longer growth periods, up to four weeks, while others, especially the yeasts, required only six to ten days.

Seven hundred and fifty milliliters of the medium were placed in Florence flasks of 3,000 ml. capacity. The organism to be tested was first grown on Sabouraud agar. From this growth a heavy saline suspension was prepared by trituration, and 3 ml. of this suspension was added to the medium in the Florence flasks, which were loosely stoppered with nonabsorbent cotton covered with aluminum foil. The flasks were then placed on an agitating machine and kept at room temperature. In a few cases, incubator temperatures were used.

At the end of the growth period, the liquid was filtered through a Seitz filter (E. K.). The resulting filtrate was placed in viscosine tubing, and the volume was reduced to 25 per cent of the original by pervaporation in the air stream from a fan. The concentrated filtrate was refiltered, checked for sterility, and set up against BCG-186 as follows.

Twenty-eight standard culture tubes, 20 by 150 mm., were racked in blocks of four. All tubes received 4.5 ml. of Dubos medium with added bovine serum albumin. Five-tenths of a milliliter of a saline suspension of BCG was added to all but four of the tubes. Each 0.5 ml. of suspension contained approximately 0.1 mg. of BCG from a fourteen-day growth on modified Löwenstein agar slants.

The culture filtrates from the fungi were then added in amounts to yield blocks of four tubes with final dilution of filtrate of 1:10, 1:20, 1:100, and 1:1,000. Four tubes received filtrate but no BCG. Four tubes received BCG but no filtrate. Controls were set up for each new batch of medium to ascertain any inhibitory or stimulating effect on the part of the medium.

Growth of BCG was recorded in three, seven, and fourteen days. In this system, the tubes receiving BCG alone always showed definite growth at three days and heavy growth in fourteen days.

In a few instances, the filtrates were not concentrated and the dilutions tested were 1:5, 1:10, 1:20, and 1:100. Most of the experiments were run in duplicate.

In no instance were filtrates with tuberculostatic activity encountered except in the case of *Tricophyton concentricum*. On two occasions filtrates from the original culture of this organism in this laboratory gave complete inhibition of BCG in dilutions of 1:10 and partial inhibition at 1:20 (using four times concentrated filtrate). Furthermore, these particular filtrates were also active and to the same degree against H37Rv streptomycin-sensitive, H37Rv streptomycin-resistant, and Phipps A-27 human strains.

Unfortunately this activity could not be reproduced in subsequent filtrates prepared from the same original cultures of *Trichophyton concentricum*. Despite numerous later attempts with variations in media, temperature, length of growth period, pH, aeration, and methods of filtration, no subsequent filtrates were active. Two other strains of *Trichophyton concentricum* were obtained, and with these results were also negative.

None of the filtrates tested against the organisms in list 2 showed any significant inhibitory properties.

In summary, a study of culture filtrates from representative strains of many of the pathogenic fungi and yeasts failed to reveal any filtrates with significant and reproducible tuberculostatic or other antibacterial activity.

Certain filtrates from *Trichophyton concentricum* showed inhibitory effects against tubercle bacilli, but a variety of experiments failed to reproduce the activity of the original filtrates.

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June 25, 1952

THE ALTERED GROWTH CHARACTERISTICS OF ISONIAZID-RESISTANT TUBERCLE BACILLI

The so-called "laboratory-adapted" strains of *Mycobacterium tuberculosis* var. *hominis*, such as the H37Rv strain, are capable of growing well in a simple synthetic medium and do not require such growth factors as vitamins.[1] It is the purpose of this communication to report the apparent need for a growth factor, as yet undefined, for the H37Rv strain of *M. tuberculosis* made resistant to isoniazid.

By a single 35-day exposure of H37Rv at 37°C. to serial dilutions of isoniazid in Dubos liquid Tween-albumin medium, a strain of *M. tuberculosis* was obtained which exhibited a thousandfold increase in resistance, with the minimal inhibiting concentration changing from 0.024 γ to 25.0 γ per ml. The growth which appeared in tubes containing 12.5 γ of isoniazid per ml. was subcultured in three types of liquid media: (*1*) a "basal" medium consisting essentially of mineral salts, asparagine, and glycerol; (*2*) the basal medium to which were added Tween 80[2] to 0.02 per cent and bovine albumin, fraction V (Armour), to 0.2 per cent; and (*3*) the basal medium with fresh bovine serum added to a final concentration of 10 per cent. Replicate tubes of these three media were also inoculated

TABLE 1

GROWTH OF ISONIAZID-SENSITIVE AND -RESISTANT H37Rv IN THREE TYPES OF LIQUID MEDIA

MEDIUM	GROWTH* AFTER 14 DAYS	
	Isoniazid-Sensitive	Isoniazid-Resistant
Basal	+++	0
Basal + Tween + albumin	++++	++
Basal + serum	++++	++++

* Degree of growth approximated by inspection

with the "parent" isoniazid-sensitive culture of H37Rv. The results of this procedure are given in table 1.

From the evidence presented in table 1, which is representative of a number of such experiments with the H37Rv strain, it appeared that on becoming isoniazid resistant this organism had lost the ability to grow in the synthetic basal medium. Since there was abundant growth in the serum medium, and, to a lesser extent, in the Tween-albumin medium, this was interpreted as indicating a growth factor requirement which was met by serum and Tween 80 or albumin. The possibility was also considered that this strain had become isoniazid dependent, but this consideration was eliminated when it was found that concentrations of isoniazid ranging from 100 through 0.00002 γ per ml. failed to support growth in the basal medium. In an attempt to define more closely the origin of the growth factor, the basal medium was enriched with a variety of substrates and was inoculated in duplicate with both the resistant and sensitive strains. The materials employed and the results obtained are presented in table 2.

From the data given in table 2, it appeared that fresh whole bovine serum provided the best substrate of those tested for the growth of the isoniazid-resistant strain. Fraction V albumin and yeast extract also permitted growth of this strain, but to a lesser degree than that occurring in serum. Because of the fact that yeast extract supported

[1] BERNHEIM, F.: Advances in Tuberculosis Research, 1951, *4*, 5.

[2] Tween 80 is the proprietary name for the polyoxyethylene derivative of Sorbitan monooleate, obtained from the Atlas Powder Co., Wilmington, Delaware.

some growth, it was postulated that a vitamin might be the growth factor. However, none of the following, when added to the basal medium in concentrations ranging from 1,000 through 0.00001 γ per ml., appeared to fulfill the particular growth requirements of the isoniazid-resistant strain of H37Rv: *p*-aminobenzoic acid, *p*-hydroxy benzoic acid, orotic acid, biotin, thiamine, riboflavin, pyridoxine, nicotinic acid, isonicotinic acid, pantothine, or inositol. Inconclusive and variable results were obtained with pantothenic acid, nicotinamide, and folic acid, and additional experiments are in progress with these compounds to establish their possible role as growth factors.

The failure of the isoniazid-resistant strain of H37Rv to grow in the basal synthetic liquid medium has been consistently observed in this laboratory in repeated experiments. It should be mentioned that only those strains manifesting greater than a five hundred fold increase in resistance appeared to lose the ability to grow in the basal medium. Strains of a lesser degree of resistance, however, did grow in the basal medium, but even these grew more slowly than the parent sensitive strain. The fact that some

TABLE 2

GROWTH OF ISONIAZID-RESISTANT AND -SENSITIVE H37Rv IN THE PRESENCE OF VARIOUS SUBSTRATES

BASAL MEDIUM PLUS	PER CENT CONCENTRATION SUBSTRATE*	GROWTH AFTER 14 DAYS	
		Isoniazid-Sensitive	Isoniazid-Resistant
Serum	10.0–0.313	++++	++++
Tween 80	0.1–0.013	++	0
Fraction V albumin (Armour)	4.0–0.125	+++	+++
Crystalline albumin (Armour)	4.0–0.125	+++	0
Casein hydrolysate†	1.0–0.03	+++	0
Yeast extract‡	0.5–0.03	+++	++

* Concentrations prepared as twofold serial dilutions

† Difco vitamin-free casamino acids

‡ Difco autolyzed fresh yeast

isoniazid-resistant strains grow more slowly than the parent strain was reported for *M. ranae* by Szybalski and Bryson.[3] The failure of isoniazid-resistant strains of H37Rv to grow on subculture has also been reported by Karlson and Ikemi.[4] The latter employed an egg-yolk–agar medium and noted that, of 18 isoniazid-resistant colonies studied, 5 failed to grow on subculture. It is likely that their experience was similar to that in the present studies in that a growth factor requirement had developed with the acquisition of isoniazid resistance and that their egg-yolk medium did not contain the growth factor. A puzzling aspect of this phenomenon, however, is the fact that their resistant colonies were *originally* capable of growth on what apparently was a deficient medium for such organisms. It may be possible that, if a growth factor was involved, it was needed in trace amounts and was present in the inoculum of sensitive organisms.

From an applied viewpoint, the implications of this phenomenon are of some significance. For example, in a study of the occurrence of isoniazid-resistant organisms isolated from treated patients, at least a serum-enriched medium should be employed. Furthermore, as pointed out by Szybalski and Bryson,[3] the more rapidly growing izo-

[3] SZYBALSKI, W., AND BRYSON, V.: Am. Rev. Tuberc., 1952, *65*, 768.

[4] KARLSON, A. G., AND IKEMI, Y.: Proc. Staff Meet., Mayo Clin., 1952, *27*, 239.

niazid-sensitive members of a population of *Mycobacteria* could overgrow the resistant cells and thus give the appearance of instability or reversibility of isoniazid resistance. In this connection, the present writer has been unable to confirm the observation by Pansy and associates[5] that resistance to isoniazid is rapidly lost. The highly resistant strain of H37Rv has been maintained in a serum-enriched isoniazid-free medium through seven transfers made at weekly intervals (involving approximately 100 bacterial generations) without any evidence of loss or decrease in the degree of isoniazid resistance.

A second application of this growth factor requirement is that it provides a means of distinguishing between isoniazid-sensitive and isoniazid-resistant tubercle bacilli without having to use isoniazid as the selective agent. This may prove to be useful in such studies as the genetics involved in isoniazid resistance.

Of more fundamental importance is the elucidation of the chemical nature of the hypothetical growth factor. If this can be done, it may illuminate the metabolic basis for the development of isoniazid resistance. Moreover, such information might provide a clue to the mode of action of isoniazid on sensitive tubercle bacilli. In so far as chemotherapy is concerned, the growth factor requirement of isoniazid-resistant cells might render them more susceptible to inhibitors, particularly those modeled as analogues of the growth factor. Indeed, the combined use of such an inhibitor with isoniazid should suppress or eliminate the emergence of resistant tubercle bacilli.

It should be pointed out that the development of a growth factor requirement associated with the acquisition of drug resistance is not an unusual circumstance. In their chapter on mechanisms of drug resistance, Work and Work[6] present a number of examples of this phenomenon, involving alternative metabolic pathways. The failure of isoniazid-resistant strains of tubercle bacilli to grow in the basal medium employed in these studies may well rest on a similar basis.

From the evidence on hand, it appears that the growth factor in those materials assayed is present in sufficient amount only in serum and fraction V albumin, with a lesser or less available amount in yeast extract. It may be significant that crystalline albumin does not support the growth of the isoniazid-resistant organisms, in contrast to fraction V albumin. This suggests that the factor is not serum albumin per se but, instead, exists as a contaminant or impurity associated with fraction V albumin which is removed in the process of purification of albumin.

In summary, it has been demonstrated that the H37Rv strain of *M. tuberculosis* var. *hominis* made resistant to isoniazid has lost the ability to grow in a synthetic liquid medium. This strain grew as well as the parent sensitive organisms in the same medium enriched with fresh bovine serum or fraction V albumin. From the results of such experiments, it has been postulated that a growth factor requirement has occurred concurrently with the acquisition of resistance to isoniazid. This factor does not appear to be one of the more commonly known vitamins or amino acids. The implications of this phenomenon are discussed.

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[5] PANSY, F., *et al.*: Am. Rev. Tuberc., 1952, *65*, 761.
[6] WORK, T. S., AND WORK, E.: Interscience Publishers, Inc., New York, 1948.

BIOLOGY OF TUBERCLE BACILLI IN NECROTIC LESIONS

Bacteriologic examination of resected lung specimens has shown recently that, while smear of the caseous material from an encapsulated lesion may contain numerous tubercle bacilli, it is not often possible to obtain growth on culture or to produce progressive disease in the guinea pig. There are two schools of thought regarding the state of these bacilli; some workers consider them to be dead while others take the more cautious view that they may be capable of revival, a phenomenon that has been observed in certain other seemingly nonviable organisms. In view of the theoretical and practical importance of this controversy, it might be helpful to consider some of the fundamentals involved in the life and death of bacteria.

The ability of a bacterium to multiply is the bacteriologist's best criterion of viability. When this property is permanently lost and can no longer be restored by any known means, the bacterial cell may be considered dead. It is difficult to ascertain the exact point at which the bacterium loses the power of reproduction since this is the result of a gradual chemical process which may be reversible up to a certain point, either by removal of the destructive factor or by exposure of the cell to a specific physicochemical environment.

The known examples of resuscitation of apparently "killed" bacteria are few and were accomplished under certain specific conditions. Kelner[1, 2] discovered that the lethal action of ultraviolet light can be reversed by exposure of the "killed" bacilli to visible light. Not all of the irradiated cells can regain their viability. The percentage of recovery is dependent upon the original ultraviolet dose. Given a sufficiently high dose of ultraviolet, none of the cells can be revived no matter how long they are exposed to the reactivating light.

Certain bacteria treated by heat under specific conditions may be considered "dead" in one medium while they can be revived in another medium. Similarly, bacteria treated with a toxic agent may remain incapable of multiplication even after the cells are washed thoroughly, but the addition of antidote, which combines with the poison in the protoplasm, may revive the cell if administered in time.[3] *Staphylococci* exposed to mercury bichloride are incapable of growth when transferred to fresh medium, yet they may be revived by treatment with hydrogen sulfide.[4]

Certain microorganisms have been described which produce toxic substances that are inhibitive to their growth in the basal medium. This effect may be overcome by the addition of efficient toxin adsorbers such as charcoal or starch.[5] A mutant of *Neurospora* produces an excessive amount of *p*-aminobenzoic acid which, in the absence of sulfonamides, is indirectly toxic and prevents growth. When sufficient sulfonamide is added to the medium, growth is permitted.[6]

There are many examples of mutant bacterial strains which require specific growth factors for normal multiplication. These diverse types have been obtained from the original parent strains by various methods. Of greatest interest in this connection are the streptomycin-dependent mutants which have been isolated from parent strains of virulent tubercle bacilli, from BCG cultures, and from avirulent *Mycobacteria* as well as from many species of nonacid-fast microorganisms. One might consider these de-

[1] KELNER, A.: Proc. Nat. Acad. Sc., 1949, *35*, 73.

[2] KELNER, A.: Bull. New York Acad. Med., 1950, *26*, 189.

[3] RAHN, O.: Physiology of Bacteria, The Blakiston Company, Philadelphia, 1932, p. 270.

[4] DUBOS, R. J.: J. A. M. A., 1944, *124*, 633.

[5] POLLOCK, M. R.: Symposia No. III: Selective Toxicity and Antibiotics, Academic Press Inc., New York, 1949, p. 193.

[6] ZALOKAR, M.: Proc. Nat. Acad. Sc., 1948, *34*, 32.

pendent forms "dead" with regard to streptomycin-free medium and even animal inoculations;[7] yet they are "alive" on medium which contains streptomycin. In this instance the definition of life and death becomes the "function of the test medium."

The foregoing facts offer some justification for the bacteriologist's cautious attitude in the interpretation of bacterial life and death. It can be said, however, that the bacterial cell can, under the impact of unfavorable environmental forces, cease to multiply, both *in vitro* and *in vivo*, and subsequently lose permanently the power of reproduction.

As indicated in the introductory paragraph, this discussion is concerned with the physiologic state of the tubercle bacilli present in closed lesions, which fail to grow or to produce disease in guinea pigs. The subject will be treated in the light of available knowledge and some recent information obtained in this laboratory.

It has been demonstrated that chemotherapeutic agents per se need not be directly responsible for the nonviability of the tubercle bacilli present in the closed lesion, since similar results were obtained in patients not receiving drug therapy prior to surgery. All of these patients had stable lesions, as revealed by roentgenography and examination of the sputum for tubercle bacilli.[8] Moreover, the present writer has not been successful in demonstrating streptomycin or para-aminosalicylic acid (PAS) in the closed lesions removed from patients who took these drugs.

Another significant consideration in relation to "positive" smear and "negative" culture is the age and morphology of the lesion. In older closed lesions, the incidence of cultures positive for *M. tuberculosis* was far less than in the open cavities, even in the same patient. It seems reasonable to assume that, when the lesion is closed, either by natural means or aided by drugs, an unfavorable environment is created for the normal multiplication of tubercle bacilli in or around the lesion. Once multiplication ceases, disruption of the normal physiology of the cells occurs and finally death ensues. The writer has kept suspensions of tubercle bacilli in liquid Tween medium stored at refrigerator temperature, and periodic viability tests revealed that within two years only a few cells of an original viable population of 10 million per ml. were capable of growth. The virulence and growth requirements of the surviving cells were not affected. Attempts to revive the nonviable cells or to demonstrate a possible evolutionary change in growth requirements were unsuccessful. Apparently, in this environment the cells ceased to multiply and gradually died of senescence even though the food supply was ample. Admittedly, the environmental effects to which the tubercle bacilli are subjected in the encapsulated caseous lesion are more complex than in the relatively simple condition cited.

The possibility of fermentation products of the bacilli or toxic tissue constituents being adsorbed or absorbed by the bacilli was also considered. It was thought that the cells might be revived if freed of these products, and, therefore, the caseous material was washed repeatedly with physiologic salt solution and subsequently inoculated on media containing efficient adsorbing agents (charcoal, albumin, and starch). No growth was obtained on these media in any instance in which it was not also present on the medium employed routinely.

The failure of tubercle bacilli to grow on media which ordinarily support good growth or to produce disease in guinea pigs might conceivably be due to evolutionary changes resulting from natural selection of spontaneously occurring mutants affecting one or more properties of the organism. Possible alteration of the nutritional requirements of the bacilli was studied in some detail. A variety of simple and complex media having different pH values were inoculated and incubated at different temperatures. In several

[7] Vanderlinde, J. R., and Yegian, D.: Am. Rev. Tuberc., 1951, *63*, 96.

[8] Beck, F., and Yegian, D.: Am. Rev. Tuberc., 1952, *66*, 44.

instances a portion of the caseous material was incorporated in the basal medium prior to inoculation on the assumption that this might supply an essential growth factor. As an apparent growth-stimulating effect of certain contaminating bacteria and fungi on tubercle bacilli has been observed in this laboratory, variety of bacteria and soil fungi were tested in this respect. None of these studies proved rewarding.

It is conceivable that, in the course of development of a tuberculous lesion, interaction of the host and local inflammatory tissue constituents might bring about hereditary changes in a certain number of tubercle bacilli, giving these a great biologic advantage over the remainder of the bacterial population. Presumably, this variant might eventually predominate in the local tuberculous environment. This hypothesis was investigated *in vitro* by adding viable tubercle bacilli to caseous material and testing the properties of the added cells by appropriate methods. Even after several weeks of exposure to the caseous material, the bacilli grew well on the usual media and there was no change in pathogenicity. Obviously, the highly artificial conditions of this experiment are only roughly analogous to those in the tuberculous lesion, and yet it is shown that tubercle bacilli are not permanently altered by the caseous material per se.

It is clear that the closed lesion provides an unfavorable environment for the survival and multiplication of tubercle bacilli, but there is little factual explanation for the mechanism involved in the death of tubercle bacilli or their gradual disappearance in necrotic areas. It is important to consider the genetic constitution of the host and the pathogen as well as the multitude of environmental factors which operate in such a complex biologic system.

In conclusion, there is no evidence on which to base the belief that the tubercle bacilli present in caseous material, which will not grow or produce disease in guinea pigs, can be revived. Perhaps in the future the discovery of new biologic procedures may provide additional means of reviving the disorganized cell, but at the present time the differentiation between life and death must rest upon the knowledge available.

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August 7, 1952

CONTROL STUDY OF COMPARATIVE EFFICACY OF ISONIAZID, STREPTOMYCIN-ISONIAZID, AND STREPTOMYCIN–PARA-AMINOSALICYLIC ACID IN PULMONARY TUBERCULOSIS THERAPY

I. Report on Twelve-Week Observations on 526 Patients

Whether "the drug of promise" was also to become the drug of choice was the question posed early this year by the favorable reports of the first clinical use of isoniazid in the treatment of tuberculosis. The usefulness of the new drug in comparison with streptomycin and para-aminosalicylic acid was still untested. In April, 1952, the Public Health Service, Federal Security Agency, in cooperation with twenty-two tuberculosis hospitals throughout the country, began an extensive, rigorously planned investigation[1] of the comparative merits of isoniazid alone, isoniazid in combination with streptomycin, and streptomycin with para-aminosalicylic acid (PAS) in more than 1,500 cases of pulmonary tuberculosis.

The participating clinical investigators[2] and the Public Health Service formulated a protocol governing the management of all patients in the study in the cooperating hospitals. Uniform observations made at four-week intervals are submitted to the Public Health Service, which serves as the coordinating center. This preliminary report on the bacteriologic, roentgenographic, and clinical changes which occurred during the first twelve weeks of a forty-week treatment period includes the data on 526 patients selected during the first three weeks of the study.

In the present report, "probable bacterial sensitivity to streptomycin" has been estimated on the basis of the amount and date of streptomycin therapy prior to study. Actual determinations from cultures sent to the Trudeau Laboratory[3] will be available for later analyses. Meanwhile, the estimations have been used to separate the cases grossly into those with "probably streptomycin-sensitive" and "probably streptomycin-resistant" tubercle bacilli.

The initial composition of the "streptomycin-sensitive" and "streptomycin-resistant" groups is very similar with respect to age, race, sex, and clinical characteristics. Approximately two-fifths were between fifteen and thirty-five years of age, another two-fifths were between thirty-five and fifty-five years, and one-fifth were more than fifty-five years. Approximately three-fifths of the patients were white and a similar proportion

[1] The isoniazid for this investigation was generously supplied by E. R. Squibb & Sons as Nydrazid.

[2] Drs. F. H. Alley, E. Bowerman, and S. C. Carter, Tennessee State Tuberculosis sanatoriums at Memphis and Oakville, Tenn.; Dr. P. T. Chapman, Herman Kiefer Hospital, Detroit, Mich.; Dr. S. S. Cohen, Glen Lake Sanatorium, Oak Terrace, Minn.; Dr. H. G. Curtis, Sunny Acres Tuberculosis Hospital, Cleveland, Ohio; Dr. R. Davies, Firland Sanatorium, Seattle, Wash., Dr. F. P. Dawson, Middlesex County Sanatorium, Waltham, Mass.; Dr. R. Hofstra, USPHS Hospital, Brooklyn, N. Y.; Drs. W. L. Howard and W. J. Steininger, Maybury Sanatorium, Northville, Mich.; Dr. G. E. Martin, Pittsburgh Tuberculosis Hospital, Pittsburgh, Pa.; Dr. H. M. Payne, Freedmen's Hospital, Washington, D. C.; Dr. R. F. Payne, Battey State Hospital, Rome, Ga.; Dr. M. B. Pianetto, Robert Koch Hospital, Koch, Mo.; Drs. H. C. Sweany, B. L. Brock, and W. L. Potts, Florida State sanatoriums at Orlando and Lantana, Fla.; Drs. H. S. Willis, H. F. Easom, W. H. Gentry, and C. D. Thomas, North Carolina State sanatoriums at Wilson, McCain, and Black Mountain, N. C.; Dr. G. C. Wilson, Uncas-on-Thames Sanatorium, Norwich, Conn.; and Drs. J. L. Wilson, H. C. Dooling, G. M. Eckley, and H. W. Weest, Pennsylvania State sanatoriums at South Mountain, Cresson, and Hamburg, Pa.

[3] Under the direction of William Steenken, Jr.

male. Information on the recency of disease indicates a greater proportion of "chronic" cases in the "streptomycin-resistant" group. Of the resistant group, 90 per cent have far advanced disease and less than one per cent were first hospitalized within the past year. The corresponding proportions in the sensitive group were 70 per cent and 40 per cent.

TABLE 1

PERCENTAGE DISTRIBUTION OF OPINIONS OF ROENTGENOGRAPHIC CHANGES IN CASES CLASSIFIED BY TREATMENT REGIMEN AND PROBABLE STREPTOMYCIN SENSITIVITY AT FOUR, EIGHT, AND TWELVE WEEKS

	PROBABLY STREPTOMYCIN SENSITIVE				PROBABLY STREPTOMYCIN RESISTANT			
	Total Per Cent	Improved*	No Change†	Worse‡	Total Per Cent	Improved*	No Change†	Worse‡
Streptomycin-PAS								
4 weeks	100.0	3.6	94.7	1.7	100.0	—	100.0	—
8 weeks	100.0	8.3	87.8	3.9	100.0	—	94.5	5.5
12 weeks	100.0	17.9	77.3	4.8	100.0	2.8	88.0	9.2
Streptomycin-Isoniazid								
4 weeks	100.0	7.8	89.7	2.5	100.0	3.7	95.8	0.5
8 weeks	100.0	19.0	78.4	2.6	100.0	16.2	81.1	2.7
12 weeks	100.0	30.3	63.9	5.8	100.0	18.7	77.3	4.0
Isoniazid								
4 weeks	100.0	2.3	96.0	1.7	100.0	8.4	90.5	1.1
8 weeks	100.0	15.2	84.2	0.6	100.0	14.2	83.5	2.3
12 weeks	100.0	22.6	74.5	2.9	100.0	15.1	79.6	5.3

* Moderate and marked improvement
† Slight improvement, no change, and slight deterioration
‡ Moderate and marked deterioration and death

Complete objectivity in the assignment of drug therapy was ensured by strict randomization in the central office in the allocation of cases to three forty-week regimens:

Streptomycin-PAS: 1 gm. of streptomycin twice weekly plus 10 to 12 gm. of PAS daily

Streptomycin-isoniazid: 1 gm. of streptomycin twice weekly plus 150 to 300 mg. of isoniazid daily

Isoniazid: 150 to 300 mg. daily

This method of chance allocation produced a subdivision of the "streptomycin-sensitive" cases into three very similar regimen groups except that the streptomycin-PAS group contained fewer febrile patients. Likewise, the three drug groups of "streptomycin-resistant" cases were initially similar in composition.

Roentgenographic evaluation

Roentgenograms for each case, obtained at the time of selection and after four, eight, and twelve weeks of therapy, have been evaluated independently by three persons. Each clinical investigator judged an equal number of cases other than his own from each

treatment group without knowledge of the drug regimen or the originating hospital. The resulting 1,578 opinions on roentgenographic changes which occurred in 526 patients have been analyzed as representing the change in roentgenographic status of patients

TABLE 2

PROPORTION OF UNIMPROVED CASES, CLASSIFIED BY TREATMENT AND BY PROBABLE STREPTOMYCIN SENSITIVITY, AT FOUR, EIGHT, AND TWELVE WEEKS

	PROBABLY STREPTOMYCIN SENSITIVE			PROBABLY STREPTOMYCIN RESISTANT		
	Streptomycin PAS	Streptomycin Isoniazid	Isoniazid	Streptomycin PAS	Streptomycin Isoniazid	Isoniazid
Number of cases	122	109	120	53	63	59
Per Cent Bacteriologically "Positive"*						
Selection	63.1	69.7	62.5	67.9	77.8	67.8
4 weeks	49.2	38.3	36.1	62.0	51.6	37.3
8 weeks	40.2	29.5	29.1	53.1	48.4	33.9
12 weeks	37.1	21.4	29.8	52.2	50.8	37.9
Per Cent with Copious Sputum						
Selection	23.0	22.9	20.0	17.0	23.8	25.4
4 weeks	23.3	23.1	19.3	18.0	17.5	23.7
8 weeks	24.8	21.9	24.8	24.5	19.4	25.4
12 weeks	23.8	12.6	14.9	23.4	16.4	13.8
Per Cent Febrile†						
Selection	12.3	28.4	22.5	15.1	17.5	11.9
4 weeks	12.5	10.2	12.7	14.0	7.9	10.2
8 weeks	18.6	12.3	16.1	14.3	9.7	11.9
12 weeks	16.2	12.6	12.3	17.0	4.9	10.3
Per Cent Underweight‡						
Selection	51.2	48.6	49.2	50.9	58.7	55.9
4 weeks	46.6	45.8	42.4	49.0	58.7	47.5
8 weeks	45.0	40.6	41.0	46.9	50.0	42.4
12 weeks	45.2	37.6	35.4	47.8	50.0	39.3

* Based on microscopic examination of sputum smears; reports on cultures planted concurrently not yet available.

† Median of highest oral temperature for five days: febrile 99.0°F. and above

‡ Minus deviation of more than 10 per cent from standard height-weight values

in each of the six groups. The categories of change were condensed for table 1 to a three-point scale, *significant improvement, essentially no change*, and *significant deterioration.*

Sputum, fever, and body weight

The factors of bacteriologic status, amount of sputum, temperature, and body weight all lend themselves to a simple dichotomy: positive and negative sputum smears, copious and less than copious amount of sputum as judged by each institution, febrile and afebrile

(less than 99.0°F.), normal and underweight (minus deviation of more than 10 per cent from standard height-weight values). For each of these factors, the condition of a patient may be described, at any particular point in time, as either favorable or unfavorable. Although every case of active pulmonary tuberculosis possesses the potentiality for favorable roentgenographic change, patients who have "negative" sputum smears, little or no sputum, no fever, or normal weight cannot show further radical improvement on these points. The groups under investigation contained large numbers of patients who at selection had already attained this favorable state. Therefore, in table 2 the results of the three drug regimens are compared by presenting the proportion of each group in an unfavorable state at succeeding points in time.

Deaths

Among those classified as unfavorable are 4 patients, all presumed to have streptomycin-sensitive infections, who died during the first twelve weeks of treatment. Two of the deaths occurred in the streptomycin-PAS group, the culmination of the tuberculous process. The other 2 deaths were in the streptomycin-isoniazid group, one from cerebral hemorrhage in a 75-year-old patient and the other from myocardial infarction.

The most definite statement that can be derived from the study so far is that pulmonary tuberculosis moves only very slowly when its progress is measured without bias in objective terms on groups of patients. This seems to be the case even when patients are given the best treatment known today, including the newly discovered isoniazid. There are indications that patients who already have had streptomycin make better progress when their treatment is continued with isoniazid than with more streptomycin and PAS. Patients who have not had streptomycin, as a group, improve when treated with any of the three drug regimens used here, but there is no compelling evidence at the end of the first three months that one regimen is better than another.

DIVISION OF CHRONIC DISEASE AND TUBERCULOSIS
PUBLIC HEALTH SERVICE
FEDERAL SECURITY AGENCY
WASHINGTON, D. C.

FRANK W. MOUNT
SHIRLEY H. FEREBEE

September 17, 1952

Books

WHEN DOCTORS ARE PATIENTS. By Max Pinner and Benjamin F. Miller. Pp. 364, W. W. Norton & Company, New York, 1952, Price, $3.95.

This book has special interest for readers of THE AMERICAN REVIEW OF TUBERCULOSIS for two reasons. It was initiated and organized by a former editor of the REVIEW, the late Max Pinner, and one of its twenty-three chapters describes the reaction of a physician to tuberculosis in his own case.

Max Pinner, who died in 1948 after a long and losing battle from the sequelae of acute rheumatic fever, has written an absorbing chapter on his own compromise with the limitations imposed by increasing dyspnea, angina, and other symptoms of progressive heart disease. The keynote of the volume is truly presented in this chapter in its account of the essential adjustments an industrious and unselfish physician, unusually competent and mentally qualified for great and increasing achievement, had to make in the face of the inexorable advance of a fatal disease. The spiritual peace achieved in the final surrender reminds one of the last chapters of the autobiography of Edward L. Trudeau.

The chapter on a doctor's reaction to his own tuberculosis is written by a physician who does not identify himself and writes under a pseudonym. It relates the not uncommon story of a patient with minimal disease who achieved an insecure arrest, suffered a relapse, "took the cure" again in earnest, and finally made what appears to be a lasting recovery. It is developed chiefly from the psychiatric point of view in a story of emotional upset and final recovery of stability, peace of mind, and wisdom. Probably no two physicians would describe their experience with tuberculosis in the same way, nor is it likely that a single individual would react in the same way at different times in his life. These comments hold for the entire volume. The individual chapters reflect, not what doctors as a class do and feel when they are sick, but what a particular doctor did under particular circumstances. Individual expression gives this book much of its interest. Dr. Benjamin Miller, who took up the task of editing after Dr. Pinner's death, has rendered faithful and creditable service to his former Chief, and the book is appropriately dedicated to Dr. Pinner's widow, Berna Pinner.

ESMOND R. LONG
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LIFE STRESS AND BODILY DISEASE. Edited by Harold G. Wolff, Stewart G. Wolf, and Clarence C. Hare. Pp. 1,135, The Williams & Wilkins Company, Baltimore, 1950, Price, $15.00.

Under the title, *Life Stress and Bodily Disease*, the twenty-ninth volume of the research publications of the Association for Research in Nervous and Mental Diseases purports to present "a criticism and review of the methods of study, observations and prevailing concepts concerning man's reactions to stress" (page xiii). "Anything may be considered a stress if it threatens the biologic integrity of an organism either directly by its physical or chemical properties or indirectly because of its symbolic meaning" (page 125).

The intellectual leadership and the professorial discipline exercised by Harold G. Wolff, President of the Association and Editor-in-Chief of this volume, have had a salutary effect on most of the 132 contributors, and the symposium is remarkable in that the objectives stated in the preface above have been realized to an unusual degree.

In the first section, previous investigations, most of them undertaken with different aims in view, are re-examined by the authors in an attempt to elucidate the mechanisms involved in stress. Richter reports on the anatomic, physiologic, and behavioral modifications which have taken place in the Norway rat after breeding for several generations in the laboratory, which would make survival in the "stresses" of a wild environment almost impossible. (This observation leaves the reader free to speculate happily and unscientifically about the possibilities of man's losing his capacity to adapt to a variety of physical stresses after living in air-conditioned houses!) Not only are observations reported on the diminished capacity to react to stress of the sympathectomized and the lobotomized patient, but also a full account is given of the development of a peptic ulcer in the husband and schizophrenia in the daughter of a woman who manifested a complete personality change following lobotomy for intractable pain. In other words, homeostasis is a social as well as a biologic phenomenon, and the results of a surgical procedure undertaken on one individual for valid medical and surgical reasons may put other members of the family under such stress that these individuals will become ill.

Parts three through twelve are taken up with reports on clinical investigations and observations on life stress and headache; disorders of growth, development, and metabolism; and diseases of the eye, airways, skin, stomach, colon, muscles, joints, periarticular structures, cardiovascular system, and genital tract. While these essays are too numerous to discuss individually, they offer a "precis" and "mise au point" of up-to-date information for current use and for the guidance of future investigators. The discussions at the end of each paper furnish interesting sidelights on the attempts to reintegrate differentiated medical and social disciplines—the psychoanalyst becomes acquainted with the kymograph, the internist turns to the anthropologist for information on culture, the pediatrician correlates measurements of physical growth and development in children on the Wetzel Gred with social and economic factors.

In the opinion of this reviewer, the material on hypertension appears the most diffuse; while the observations on the gastric and colonic function in fistulous subjects are now classic. Hinkle's studies in diabetes present new and precise data in the form of experimental evidence that "stimuli arising out of the life experience of the individual, which were either consciously or unconsciously interpreted by him as threats to his security have produced in both diabetic and nondiabetic humans a rise in the ketone bodies in the venous blood and fluctuations in the blood sugar level" (page 385).

Of special interest to the physician caring for patients with chest diseases is Stevenson's report on the quantitative changes in bronchial secretion as observed in a patient with bronchiectasis in periods of depression.

Throughout the symposium, the question is asked: "Why do some people get one thing, and others another?" or "Why and what of the specificity of physiologic system or organ response?" The second section, designed to deal with this subject, is not illuminating. Nevertheless, some light is shed on the problem of specificity from a somewhat different angle. Holmes, Treuting, Grace, Wolf, Stevenson, and Duncan, all of whom have been associated with Harold Wolff at some time, present experimental evidence indicating that a pattern of physiologic hyperfunction in the respiratory, cardiovascular, and gastrointestinal systems is found in association with a pattern of behavior and a feeling state which differ conspicuously from the behavior and the feeling state associated with hypofunction in that same system.

Hyperfunction and hypofunction in a physiologic system are interpreted by Wolff as forming part of the biologic pattern of offense and defense by which the human organism endeavors to meet emergencies and deal with crises of whatever nature. Since both daily

experience and observations made under controlled laboratory conditions indicate that vomiting and diarrhea may be the reaction to the ingestion of a noxious agent and also to a "mother-in-law," it would appear that the adaptive and protective capabilities of the organism are limited and that the same biologic pattern of ejection-riddance which is used appropriately by the gut to dispose of the "bad oyster" is brought into action inappropriately in an attempt to deal with the "mother-in-law." That is to say, "the response to a variety of noxious agents in any given man may be similar, the form of this reaction depends more upon the *individual's nature and experience* than upon the particular noxious agent evoking it" (page xiii).

The formulation of "protective patterns of defense," like any other synthesis, has its limitations. It will not satisfy those who float in the limbo of the unconscious or those who believe it is unscientific to seek an interpretation which lies beyond the limits of the laboratory. But for the practitioner who is trying to take care of a sick man and to understand him, it is illuminating to find one's clinical hunches confirmed by a group of "distinguished" investigators, and to learn that "man's reactions to threats or to symbols of danger especially when sustained" may lead to tissue damage. Indeed "many aspects of disease may be looked upon as functions of man's goals, his methods of achieving them, and the conflicts they engender" (page 1088). Man may not reach for the stars with impunity.

Beatrice Bishop Berle
New York, New York

Essentials in Diseases of the Chest for Students and Practitioners. By Philip Ellman. Pp. 400, Oxford University Press, New York, 1952, Price, $6.50.

Dr. Ellman has presented in this brief and elementary book descriptions of rare as well as common intrathoracic diseases with, on the whole, judicious distribution of emphasis and division of space. The contents include, in addition to discussions of disease states and therapy, a short outline of pulmonary physiology and anatomy and descriptions of special diagnostic and therapeutic procedures. The text is copiously illustrated with roentgenograms and diagrams.

The quality of the treatment of the various subjects is, on the whole, good, especially in the cases of industrial diseases, neoplasms, and tuberculosis, to which the author devotes approximately one-fifth of the text. Nontuberculous pulmonary infections are well presented although this reviewer thought that, within the scope of the book as it is planned, the clinical features and differential diagnosis of the pneumonias might advantageously have received more space. In some instances, as one must expect in short surveys of this sort, brevity has minimized the usefulness of the discussions and, occasionally, as in the case of pulmonary sarcoidosis, undoubtedly will create misconceptions and confusion for the elementary reader.

The sections devoted to therapy are, in general, excellent, with the exception of the management outlined for emphysema and cor pulmonale, in which the author recommends prolonged oxygen therapy without cautioning the reader about its hazards in such patients. Many clinicians might quarrel with his position that digitalis is of doubtful value and perhaps harmful in cardiac failure in the emphysematous patient.

As an elementary guide to diagnosis and treatment, this book should prove useful to the student and general practitioner.

William U. Cawthon
Charlottesville, Virginia

DIE KLINIK DER TUBERKULOSE ERWACHSENER. By Von Alfred Frisch. Pp. 415, with illustrations, Springer-Verlag, Vienna, Austria, 1951, Price, $10.70.

Doctor Frisch has written a very extensive account of the clinical aspects of pulmonary tuberculosis in the adult, with a less detailed study of other pulmonary diseases and extrapulmonary tuberculosis. The book is well documented with case histories to demonstrate points which the author is attempting to make.

The author, a pupil of W. Neumann, devotes much time to the comparison of his views with those of his teacher, who had written a similar textbook several decades previously.

The details in procedures throughout, including laboratory examinations and treatment, impress one with the fact that the author is attempting to make this work a guide to the diagnosis and treatment of pulmonary tuberculosis. There is also an extensive review of the indications and a review of the different surgical procedures in the treatment of pulmonary tuberculosis. This is best demonstrated in the great stress which he places on the minute details of the physical examination. These minutiae may be necessary for students and beginners in the disease, but seem unnecessary for men practicing this specialty.

In his discussion of his experiences with streptomycin therapy, the author reports experiences similar to those which have appeared in the American literature in the past few years. The author touches only lightly on the other forms of antibiotic therapy, presumably because of his much greater experience with streptomycin.

A chapter on the pathology of tuberculosis is written by Dr. Richard Wiesner and is modeled very much along the lines of the textbook on the pathology of tuberculosis written by Dr. Paul Huebschmann twenty-three years previously. It includes many of the older views which have been long since discarded by many pathologists. It follows the Ranke classification and does form a good basis for the subsequent clinical discussion.

The book contains no bibliography or author index, but does contain a subject index.

OSCAR AUERBACH
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BOOKS RECEIVED

TUBERCLE BACILLUS AND LABORATORY METHODS IN TUBERCULOSIS. By M. A. Soltys, in collaboration with C. A. St. Hill and I. Ansell. Pp. 212, E. & S. Livingstone Ltd., Edinburgh and London, 1952, Price, $4.50.

ANNUAL REVIEW OF MEDICINE. Volume 3. Edited by Windsor C. Cutting and Henry W. Newman. Pp. 442, Annual Reviews, Inc., Stanford, California, 1952, Price, $6.00.

ADVANCES IN MEDICINE AND SURGERY from the Graduate School of Medicine of the University of Pennsylvania. Pp. 441, with illustrations, W. B. Saunders Company, Philadelphia and London, 1952, Price, $8.00.

LIVING AGENTS OF DISEASE. By James T. Culbertson and M. Cordelia Cowan. Pp. 624, with illustrations, G. P. Putnam's Sons, New York, 1952, Price, $5.50.

PRINCIPLES, PROBLEMS, AND PRACTICES OF ANESTHESIA FOR THORACIC SURGERY. By Henry K. Beecher. Pp. 65, Charles C Thomas, Springfield, Illinois, 1952, Price, $2.50.

ELEMENTS OF STATISTICS. Second Edition. By Elmer B. Mode. Pp. 377, Prentice-Hall, Inc., New York, 1951, Price, $6.35.

ILLNESS AND HEALTH SERVICES IN AN AGING POPULATION. Publication No. 170, Federal Security Agency, Public Health Service, Washington 25, D. C., Price, $0.25.

LA ANGIONEUMOGRAFIA EN LA TUBERCULOSIS PLEUROPULMONAR. By Ricardo Rimini and Aberlardo Rodriguez. Pp. 92, Facultad de Medicina de Montevideo, Instituto de Tisiologia "Prof. Dr. J. B. Morelli", Monograph No. 6, 1952.

ANNUAL REPORT FOR THE YEAR 1951, THE SOUTH AFRICAN INSTITUTE FOR MEDICAL RESEARCH. Pp. 100, The South African Institute for Medical Research, Box 1038, Johannesburg, 1951.

DER GESUNDE UND DER KRANKE KEHLKOPF IM RONTGENBILD. By C. R. Griebel. Pp. 170, Georg Thieme Verlag, Stuttgart, 1952.

TERCER CONGRESO ARGENTINO DE TISIOLOGIA, October 29–31, 1951. Pp. 519, Rosario, Argentina, 1952.

TUBERCULOSIS ASSOCIATION OF INDIA ANNUAL REPORT FOR 1951. Pp. 231, Tuberculosis Association of India, 20, Talkatora Road, New Delhi, 1952.

SEMEIOLOGIA FUNZIONALE DELLA TUBERCOLOSI POLMONARE. Edited by M. Anzalone, Pp. 351, Abruzzini Editore, Rome, 1952.

MASS BCG VACCINATION IN AUSTRIA, 1948–1950, with Special Reference to Statistics on Tuberculin Testing and BCG Vaccination. Pp. 39, The International Tuberculosis Campaign, UNICEF, 24 Rue Borghèse, Neuilly-sur-Seine, France, 1952.

MASS BCG VACCINATION IN ECUADOR, 1950–1951, with Special Reference to Statistics on BCG Vaccination and Pre- and Post-Vaccination Allergy. Pp. 41, The International Tuberculosis Campaign, UNICEF, 24 Rue Borghèse, Neuilly-sur-Seine, France, 1952.

MASS BCG VACCINATION IN TUNISIA, 1949–1951, with Special Reference to Statistics on Tuberculin Testing and BCG Vaccination. Pp. 41, The International Tuberculosis Campaign, UNICEF, 24 Rue Borghèse, Neuilly-sur-Seine, France, 1952.

American Trudeau Society

Medical Section of the National Tuberculosis Association

Report of the Committee on Therapy to the Committee on Medical Research, May 22 and 23, 1952

During the year the Committee on Therapy held two regular meetings, in New York, October 8–10, 1951; and in Boston, May 22–23, 1952. In addition, a short meeting was held, with the majority of the committee present, in St. Louis in January, 1952. Minutes of the October, 1951, meeting have previously been submitted and have been published (Am. Rev. Tuberc., 1952, *65*, 351).

At the May, 1952, meeting the following committee members were present: Drs. Robert O. Canada, David T. Carr, Robert H. Ebert, Kirby S. Howlett, Jr., Roger S. Mitchell, William M. Peck, Norman J. Wilson, and William B. Tucker, Chairman. Dr. William M. M. Kirby was unable to attend. In addition, the following members of the American Trudeau Society attended all or part of the meetings: Dr. John H. Skavlem, President; Dr. Esmond R. Long, Director of Medical Research; Dr. David T. Smith, Chairman, Committee on Medical Research; Mr. William Steenken, Jr., Chairman, Laboratory Subcommittee; Dr. Floyd M. Feldmann, Acting Executive Secretary; Dr. Donald J. Ottenberg, Assistant to the Director of Medical Research; Dr. Arthur M. Walker; Dr. Emanuel Wolinsky; Dr. H. Stuart Willis; Miss Agnes Fahy, Associate, Public Relations, National Tuberculosis Association; Miss Virginia Cameron, Medical Research Secretary; and Mrs. Martha M. Hunt.

During the year the Committee on Therapy has dealt with the following topics:

The Problem of the So-Called "Good Chronic" Case of Pulmonary Tuberculosis

In response to many requests for an official statement on this subject, the Committee undertook to survey the factors involved and constructed a statement for the American Trudeau Society, which has been published (Am. Rev. Tuberc., 1952, *65*, 643).

Laboratory Problems of Joint Interest to Clinicians and Laboratory Workers

In recognition of merging interest in many laboratory problems of tuberculosis, especially those of drug sensitivity, the Committee on Therapy met jointly with the Laboratory Subcommittee of the Committee on Medical Research twice during the year. Resultant actions from the first meeting have already been reported (Am. Rev. Tuberc., 1952, *65*, 351). In May, 1952, the committees jointly considered the problem of the effect of the hormones, cortisone and corticotropin, upon tuberculous infection (Am. Rev. Tuberc., 1951, *63*, 499).

The Effect of Cortisone and Corticotropin on Tuberculous Infection in Man

The Clinical Subcommittee of the Committee on Medical Research, together with the Laboratory Subcommittee, already had called attention to the potential hazard of treating tuberculous patients with cortisone or corticotropin (Am. Rev. Tuberc., 1951, *63*, 499). In recognition of the importance of the problem, the Committee on Therapy for 1951–1952, successor to the Clinical Subcommittee, in the fall of 1951 initiated a project for

the collection of isolated cases of persons with tuberculous infection who had received either of these agents. With the active cooperation of many physicians, clinical data and films on 81 cases were collected. On the basis of this material, a statement was published: "The Effect of Cortisone and/or Corticotropin on Tuberculous Infection in Man" (Am. Rev. Tuberc., 1952, *66*, 254), with a corresponding statement by the Laboratory Subcommittee on the effect of the same hormones in experimental tuberculosis: "The Effect of Cortisone and/or Corticotropin in Experimental Tuberculous Infections of Animals" (Am. Rev. Tuberc., 1952, *66*, 257). The Committee on Therapy for 1952–1953 plans to continue this study and to report more fully in the future.

Retrospective Studies on Therapy of Tuberculosis

Following the recommendation of earlier committees, a new subcommittee of the Committee on Therapy was established this year, the Subcommittee on Retrospective Studies on Therapy, under the chairmanship of Dr. Roger S. Mitchell. The Committee on Therapy has met jointly and worked closely with this subcommittee and has heartily endorsed its activities and recommendations. A report of the Subcommittee has been received and approved (page 643). The recommendation that the subcommittee continue its work another year has been approved by the Committee on Therapy and by the Council of the American Trudeau Society.

Isoniazid and Iproniazid

Following the release of information concerning these new drugs in the press on February 21, 1952, the Executive Committee of the American Trudeau Society, with the assistance of the Committee on Therapy, prepared a statement for immediate release to the press, which has subsequently been published in THE AMERICAN REVIEW OF TUBERCULOSIS—"Current Status of Isonicotinic Acid Hydrazide (Isoniazid) in the Treatment of Tuberculosis" (Am. Rev. Tuberc., 1952, *65*, 649).

Recent Developments in the Antimicrobial Therapy of Tuberculosis

In recognition of the broadened indications for antimicrobial therapy of tuberculosis and other developments within the year, the Committee has brought up to date its statement of a year ago: "Current Status of Antimicrobial Therapy in Tuberculosis" (Am. Rev. Tuberc. 1951, *63*, 617). This new statement on recent developments in antimicrobial therapy of tuberculosis, including the new drugs isoniazid and iproniazid, has been published: "Recent Developments in the Antimicrobial Therapy of Tuberculosis" (Am. Rev. Tuberc., 1952, *66*, 251).

The Role and Function of the Committee on Therapy in The American Trudeau Society

After a number of years of accelerating developments in the clinical fields of interest to the membership of the Society, the Committee considered it appropriate to attempt to discuss and to define the function of the Committee on Therapy within the organization of the parent Society. The Committee is grateful to members of the Society who participated in this discussion at the meeting in May; to members of the Committee on Medical Research with whom it was discussed and who approved in principle; and to members of the Council, who likewise expressed their approval. Summarizing their discussion, the Committee has prepared a statement on its role within the American Trudeau Society,

which it is hoped will be helpful to future committees and officers of the Society: "The Role of the Committee on Therapy in the American Trudeau Society" (page 644).

Respectfully submitted,

ROBERT O. CANADA
DAVID T. CARR
ROBERT H. EBERT
KIRBY S. HOWLETT, JR.
WILLIAM M. M. KIRBY
ROGER S. MITCHELL
WILLIAM M. PECK
NORMAN J. WILSON

WILLIAM B. TUCKER, *Chairman*
Committee on Therapy

Report of Subcommittee on Retrospective Studies on Therapy
May 22, 1952

The Subcommittee on Retrospective Studies on Therapy met on three occasions during the year: in October, 1951, in New York; in January, 1952, in St. Louis; and in May, 1952, in Boston. All members of the Subcommittee attended at least one meeting.

There is a recognized need for data on methods of treatment in use for the past twenty to thirty years as a baseline for comparison with present methods of treatment. A practical method for conducting retrospective studies in the various forms of therapy of tuberculosis has been evolved, and a mimeographed copy of this method is available in the office of the Executive Secretary of the American Trudeau Society. The method has been tried on a few cases from the files of the hospitals of three members of the Subcommittee. It is estimated that, if follow-up is sought and most of the information is entered by a clerk (which the Subcommittee considers feasible), a trained physician can complete 10 to 15 cases per hour, including review of pertinent chest roentgenograms.

The Subcommittee believes that, even if data were carefully collected in this manner, the yield of useful information from this type of study would be principally historical and general. Specific information permitting a good comparison of different methods of treatment would require studies of considerably more detail. It is therefore recommended that the American Trudeau Society not undertake a formal cooperative retrospective study of appreciable magnitude at the present time.

On the other hand, it is recommended that a method be developed containing enough detail to make really informative studies possible on bed rest, artificial pneumothorax, phrenic nerve operations, pneumoperitoneum, thoracoplasty, pulmonary resection, and chemotherapy. If such a method should be developed and approved, it is further recommended that its existence be publicized and that it be made available to persons interested in making retrospective studies on the variables of therapy in pulmonary tuberculosis. If standardization of such individual studies can gradually be approximated, the Subcommittee believes that it will have discharged its principal duties and functions. The Subcommittee accordingly recommends that it continue its work along these lines for another year.

Respectfully submitted,

H. H. FELLOWS
SHIRLEY H. FEREBEE
HIRAM T. LANGSTON
RUFUS F. PAYNE
W. SPENCER SCHWARTZ

ROGER S. MITCHELL, *Chairman*
Subcommittee on Retrospective Studies
on Therapy

Statement of the Committee on Therapy on the Role of the Committee on Therapy in the American Trudeau Society

The Committee on Therapy finds itself in accord with that portion of the report of the Committee on Program Development (A Policy and Trends Committee) of the National Tuberculosis Association, dated February 1, 1952, which states (on page 47 of the Report):

> We should realize that the purposes of the American Trudeau Society are broader than those of the parent organization (the NTA). The field of activity covered by the medical section (the ATS) includes the whole field of thoracic diseases, whereas the program of the national association and its affiliates is confined to the field of tuberculosis control . . . .

The Committee on Therapy believes that the interests of the American Trudeau Society, medical section of the National Tuberculosis Association, are best served by the recognition that tuberculosis is an integral part of the field of pulmonary diseases within the broad framework of internal medicine and surgery. The Committee urges that the recently appointed Program Development Committee of the American Trudeau Society thoroughly explore every avenue open to the Society to effect as complete an integration as possible in this direction. This should include consideration of broadening of the activities of the Society to include pulmonary diseases other than tuberculosis to a greater extent than at present and an increased recognition of the fundamentally close relationship which is necessary between pulmonary diseases in internal medicine and thoracic surgery.

In accordance with this principle of the unity of internal medicine and surgery, including respectively pulmonary diseases and thoracic surgery, and of the indispensability of the larger field to tuberculosis as well as of tuberculosis to that larger field, the Committee on Therapy believes that it is appropriate to attempt to define the function of this committee within the organizational framework of the American Trudeau Society.

In general, it is believed to be the function of the Committee on Therapy to represent the field of clinical medicine as related to pulmonary diseases, including tuberculosis, with respect to diagnosis and therapy, which is not directly supported by organizational elements of the Society, in the closest type of cooperation with the other major functions of the Society, medical research and education. The Committee on Therapy may be regarded as a group of internists and surgeons close to the problems of clinical medicine, intimately familiar with current investigative work in the field, who may be in a position to interpret, to evaluate, to report, and to furnish guidance on a variety of clinical problems in diagnosis and therapy for the benefit of other organizational elements of the Society and of the membership of the Society at large.

It would seem appropriate that the Committee on Therapy might, for example, fulfill the following functions:

1. To undertake to set up, guide, or organize cooperative evaluations of current or new forms of therapy
2. To analyze studies being performed in the clinical fields
3. To suggest to clinicians the significance of newer developments in the research field, serving as an interpretive agency
4. To issue statements regarding current therapeutic problems, in the light of the latest information available, for the guidance not only of the membership of the Society but of other committees of the Society

5. To assist in establishing improved standards and practices in the diagnosis of various pulmonary diseases
6. To advise the Committee on Medical Research with regard to clinical problems deserving of further investigation, and to support and even stimulate such studies
7. To work with the Committee on Medical Education on the problem of the content of curricula in medical schools and post-graduate courses
8. To assist the Medical Sessions Program Committee in the construction of balanced programs representing adequately the various emphases in diagnosis and practice in the field

As to content, it is to be re-emphasized that it is thought to be appropriate for the activities of the Committee on Therapy, as for other committees, to cover the entire field of pulmonary diseases, including tuberculosis. A brief list suggestive of the types of problem which may be appropriate for the Committee on Therapy to study in the near future could include such topics as:

The treatment of tuberculous meningitis
The management of bronchiectasis
The management of silicosis and emphysema
The treatment of childhood tuberculosis, with special reference to antimicrobial therapy
The proper management of tuberculosis among mental patients
The recognition and management of nontuberculous patients in a hospital devoted primarily to the care of the tuberculous
The role of pulmonary resection, especially localized resection, in the treatment of pulmonary tuberculosis
The clinical significance of the apparent nonviability of tubercle bacilli in resected pulmonary specimens after prolonged antimicrobial therapy
Case finding for pulmonary diseases in office practice
Encouragement of controlled studies of the effect of bed rest and of pneumoperitoneum, with antimicrobial therapy, in pulmonary tuberculosis

It is apparent that acceptance of the broadened scope of the activities of the American Trudeau Society and of the Committee on Therapy along these lines would increase the responsibility of the latter committee and would necessitate care in the selection of its personnel to provide for adequate continuity of membership. The question of administrative affiliation with existing organizational elements of the Society is secondary to the principles outlined, and the existing relationship of the Committee on Therapy with the office of the Director of Medical Research is regarded as satisfactory. But it may be that a slightly greater degree of financial support of the activities of the Committee on Therapy, chiefly for increased secretarial assistance and for utilizing the services of consultants in specialized fields, will be indicated in such an expanded program, for it may be desirable for the Committee to seek the assistance of a number of experts in connection with many of the activities it may decide to undertake.

In summary, the Committee on Therapy recommends to the Council that the newly appointed ATS Committee on Program Development be urged strongly to consider the desirability of broadening the activities of the Society to include the entire field of pulmonary diseases, as suggested; and that careful consideration be given by that committee, and by the Council, to the proposals made that the Committee on Therapy be strengthened and given a prominent role in the affairs of the Society by interpretation of develop-

ments in the clinical field of pulmonary diseases for the benefit of other committees and the entire membership of the Society.

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Committee on Therapy

Report of the Laboratory Subcommittee to the Committee on Medical Research May 23, 1952

The Laboratory Subcommittee held two meetings during the year, one in New York on October 9, 1951, and the other in Boston on May 23, 1952. A portion of each meeting was devoted to a joint session with the Committee on Therapy.

During the year the Committee revised and published in the January, 1952, issue of THE AMERICAN REVIEW OF TUBERCULOSIS a statement on methods for performing streptomycin and PAS sensitivity tests on tubercle bacilli. It also made a strong plea for more bacteriologic studies of resected tuberculous lesions from patients who had or had not received chemotherapy.

During the year, at the suggestion of the Laboratory Subcommittee to the Committee on Medical Research, Dr. Esmond R. Long, Director of Medical Research, collected information regarding the sources and methods of obtaining BCG vaccine for clinical evaluation. Statements from the directors of the three laboratories which produce and distribute the vaccine in the United States were published in the May, 1952, issue of THE AMERICAN REVIEW OF TUBERCULOSIS.

Other joint reports published by the Committee on Therapy and the Laboratory Subcommittee during the year were:

A statement on "Criteria for 'Negative' Sputum in Patients Following Antimicrobial Therapy" and one on the "Clinical Significance of *In Vitro* Determination of Streptomycin Sensitivity and Resistance," both of which appeared in the January, 1952, issue of THE AMERICAN REVIEW OF TUBERCULOSIS.

The meeting of the Laboratory Subcommittee on May 23, 1952, was attended by the following members: William Steenken, Jr., Chairman; Dr. Gladys Hobby; Lieutenant William Dye; Dr. Frank Princi; Dr. Gardner Middlebrook; and as guests: Dr. Esmond R. Long, Director of Medical Research; Dr. Karl Meyer; Dr. Emanuel Wolinsky.

At this meeting the question of bacillary resistance to isoniazid was discussed at length. It was agreed that strains of tubercle bacilli with increased drug resistance were being found in the sputum of patients with chronic cavitary pulmonary tuberculosis under therapy with isoniazid. Although the number of relatively resistant variants occurring naturally in pretreatment cultures is comparatively large, a definite increase in the isoniazid resistance of cultures obtained from treated patients may be demonstrated by serial cultures and sensitivity tests in the manner described below. It is important that sensitivity tests be performed on pretreatment cultures, as well as on cultures at frequent intervals during therapy.

It is recommended that sputum smears and cultures, as well as sensitivity tests, be performed at two-week intervals for patients being treated with isoniazid and that the permanence of isoniazid resistance be investigated by following the sensitivity tests of cultures from patients after therapy is discontinued.

It is also recommended that, whenever possible, the streptomycin and PAS sensitivity of cultures be followed from patients being treated with isoniazid whose organisms were resistant to either or both of the former drugs before therapy with isoniazid. This would bring to light any effect of isoniazid therapy on resistance to the other drugs.

Recommended Methods for Performing Isoniazid Sensitivity Tests

Isoniazid should be incorporated in the solid ATS or Löwenstein (Jensen's modification) medium (Reports of the Clinical and Laboratory Subcommittees of the Committee on Medical Research, Am. Rev. Tubere., 1952, *65*, 105) in concentrations of 0.2, 1.0, and

5.0 γ per ml. Direct sensitivity tests should be made by planting an equal amount of the processed sputum on medium containing each of the drug concentrations, as well as on two tubes containing the medium without drug. Comparison should be made of the amount of growth and the time of appearance of the growth in the drug-containing tubes with those factors in the control tubes.

Indirect or subculture sensitivity tests may be carried out by planting a suspension of tubercle bacilli or a liquid medium subculture on the same series of control and drug-containing solid medium tubes. The size of the inoculum used must be carefully standardized because of the relatively large number of resistant variants previously mentioned.

For cultures known or suspected to be resistant, a tube containing 10 γ per ml. may be included in the test.

At a joint meeting with the Committee on Therapy held on May 22, 1952, the effect of cortisone and corticotropin in human and experimental tuberculosis was discussed. Dr. Emanuel Wolinsky presented a review of 35 papers and personal communications on the use of these hormones in experimental animals. A statement on this subject has been published along with a similar statement prepared by the Committee on Therapy on the effects in humans (Am. Rev. Tubere. 1952, *66*, 257).

Respectfully submitted,

William E. Dye
Gladys L. Hobby
Gardner Middlebrook
Frank Princi
Guy P. Youmans

William Steenken, Jr., *Chairman*
Laboratory Subcommittee

NOTES

ANNUAL MEETING OF THE AMERICAN TRUDEAU SOCIETY—1953

The American Trudeau Society, medical section of the National Tuberculosis Association, invites the submission of abstracts of scientific papers for presentation at its next annual meeting in Los Angeles, California, May 18 to 22, 1953, at the Hotel Statler.

Full information can be obtained by writing to the Chairman of the Medical Sessions Committee, American Trudeau Society, 1790 Broadway, New York 19, N. Y.

ANNUAL CHEST DISEASE SYMPOSIUM

Plans for the fourth annual Chest Disease Symposium to be given January 22 and 23, 1953, at the Los Angeles County Medical Association Building, 1925 Wilshire Boulevard, are announced by Dr. Thomas H. Sternberg, representing University of California Extension.

The course will be given by the University of California Medical Extension in cooperation with the Los Angeles Tuberculosis and Health Association, the American College of Chest Physicians, and the Los Angeles Trudeau Society, and the Schools of Medicine of the University of Southern California and College of Medical Evangelists.

With program details to be announced in the near future, visiting speakers are as follows: Drs. Andrew L. Banyai, President, American College of Chest Physicians and associate clinical professor of medicine, Marquette University Medical School, Milwaukee, Wisconsin; Brian B. Blades, professor of surgery, Georgetown University, School of Medicine, Washington, D. C.; Alvis E. Greer, clinical professor of medicine, University of Texas Medical School and President-Elect, American College of Chest Physicians, Houston, Texas; H. Corwin Hinshaw, clinical professor medicine, Stanford University School of Medicine, San Francisco, California; Edgar Mayer, assistant professor of clinical medicine, Cornell University Medical School, New York, N. Y.; Sidney J. Shipman, President, National Tuberculosis Association, and clinical professor of medicine, University of California Medical Center, San Francisco, California; and Marcy L. Sussman, clinical professor of radiology, Columbia University College of Physicians and Surgeons, New York, N. Y.

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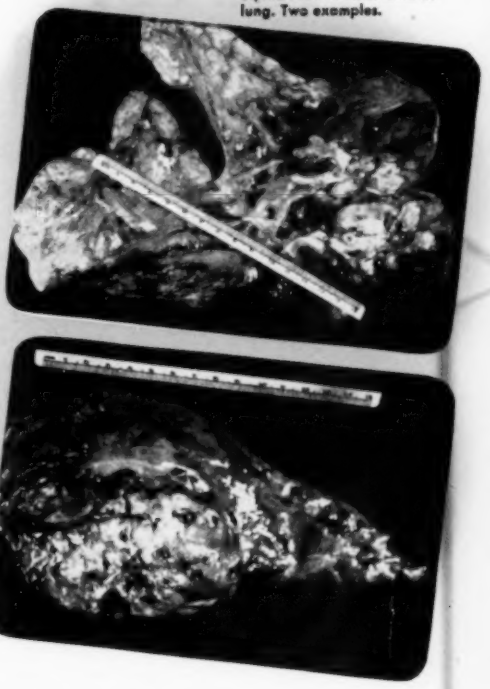

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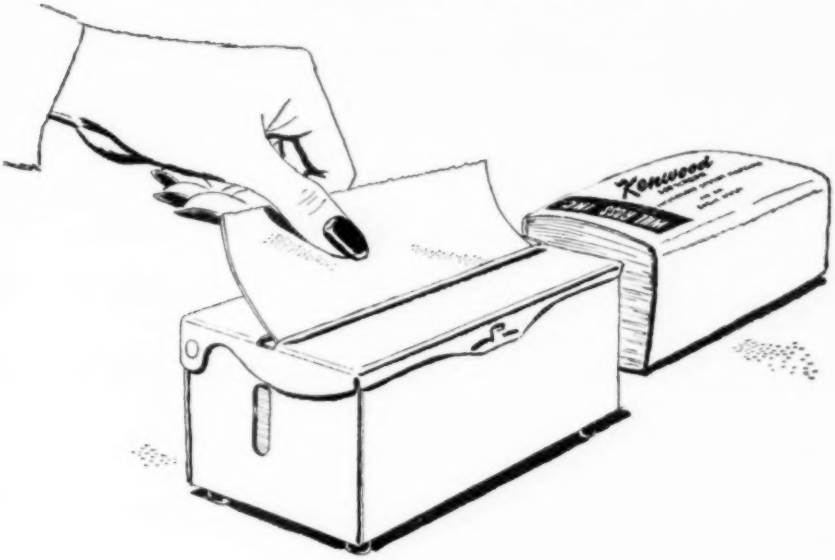

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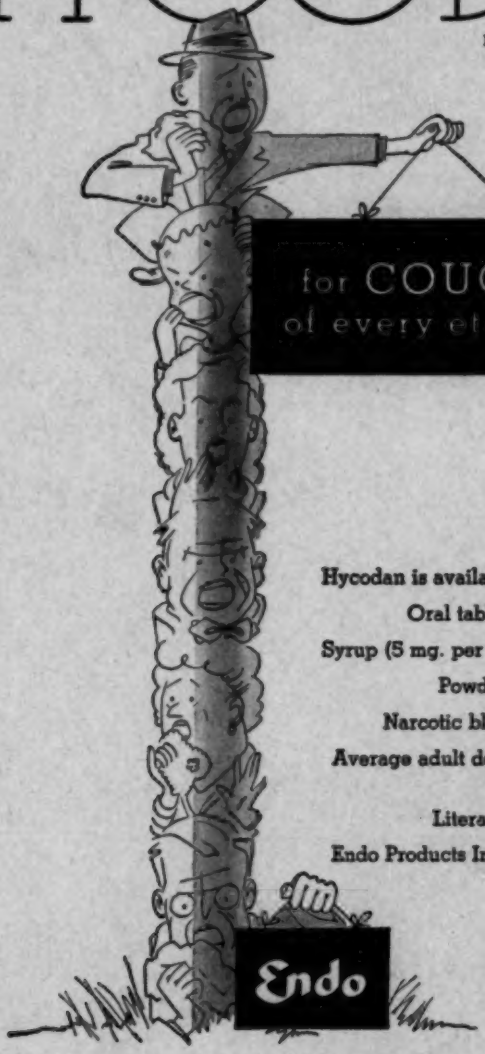

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